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Valvular heart disease: Novel epidemiological and imaging studies

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Table of Contents

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Declaration

The work in this thesis is my own, and this thesis was composed by me.

As part of the OxVALVE Study, described in chapters 2-4, I was the inaugural research fellow, and undertook the design of the research protocol, and the set up and initial scanning as described in chapter 2. I recruited and scanned a significant number of the participants, until the team of echocardiographers could be recruited and trained. The full extent of my involvement is exactly as described in the text. The statistics for this section of the thesis were performed by Eleni Frangou from the Centre for Statistics in Medicine, University of Oxford. The questionnaires described in chapter 4 were formulated in collaboration with Professor Andrew Farmer, School of Public Health and Primary Care, University of Oxford.

The work described in chapter 5 was undertaken in collaboration with centres in Leeds and Aukland, who extracted the scan data and shared it with us. I extracted the scan data from the Royal Brompton Hospital, London, and recruited, scanned and followed up the majority of the patients in the Oxford sample, who constitute the largest proportion. Specifically, I recruited, scanned, analysed, and followed up all of the patients in the sub-study of CMR and TTE. Dr Saul Myerson and Dr Theo Karamitsos helped with the statistics for this section of the thesis.

The work in this thesis has not been submitted for any other degree or professional qualification.

Abbreviations

2DTTE	Two dimensional trans-thoracic echocardiography
ACEi	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AoScl	Aortic sclerosis
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
AS	Aortic stenosis
ASE	American Society of Echocardiography
AUC	Area under the curve
BMI	Body Mass Index
BSE	British Society of Echocardiography
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCS	Canadian Cardiac Society
CFM	Colour flow mapping
CI	Confidence interval
CMR	Cardiac Magnetic Resonance
CRF	Case Report Form
CW	Continuous-wave Doppler
DNA	Deoxyribonucleic acid
EAE	European Association of Echocardiography
ECG	Electrocardiogram
EDV	End diastolic volume

EF	Ejection fraction
EROA	Effective regurgitant orifice area
ESV	End systolic volume
EU	European Union
GP	General Practitioner/Practice
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IT	Information technology
IVSd	Inter-ventricular septal thickness in diastole
LA	Left atrium
LV	Left ventricle
LVIDd	Left ventricular internal dimension in diastole
LVOT	Left ventricular outflow tract
LVSV	Left ventricular stroke volume
MI	Myocardial infarction
MR	Mitral regurgitation
MS	Mitral stenosis
NICE	National Institute for Health and Care Excellence
NIHR BRC	National Institute of Health Research Biomedical Research Centre
NYHA	New York Heart Association
OR	Odds ratio
OxVALVE PCS	OxVALVE Population Cohort Study

PIL	Patient Information Leaflet
PISA	Proximal Isovelocity Surface Area
PR	Pulmonary regurgitation
PW	Pulsed-wave Doppler
RFrac	Regurgitant fraction
ROC	Receiver operator characteristic
RVol	Regurgitant volume
RVSV	Right ventricular stroke volume
SD	Standard deviation
SOPs	Standard Operating Procedures
SSFP	Steady-State Free Precession
STAI	State-Trait Anxiety Inventory
SV	Stroke volume
TAVI	Trans-catheter aortic valve implantation
TIA	Transient ischaemic attack
TDI	Tissue Doppler imaging
TR	Tricuspid regurgitation
TTE	Trans-thoracic echocardiography
TVCLRN	Thames Valley Comprehensive Local Research Network
UK	United Kingdom
US	United States
VC	Vena contracta
VHD	Valvular heart disease

Abstract

Since living conditions have improved and antibiotics have entered routine use, valvular heart disease (VHD) in the developed world is mostly degenerative in origin, rather than rheumatic. Our population is increasing with age, and therefore the burden of VHD is likely to increase. Despite this, the epidemiology & prognostication in VHD remain poorly understood. A better understanding of the prevalence of VHD in our population, and improved methods of predicting outcomes, are essential if we are to be better equipped to meet the challenges of this new "epidemic". This thesis aims to improve our knowledge of the prevalence of VHD in the elderly, and the potential benefits of cardiac magnetic resonance (CMR) assessment of patients with clinically significant mitral regurgitation.

The prevalence of undiagnosed valvular heart disease in those aged 65 and over is examined in Chapters 2 and 3. Chapter 2 outlines a population-based screening study for VHD in primary care in Oxfordshire, which the author played a central role in establishing. The results show that VHD is extremely common in this cohort, and is strongly associated with increasing age. In chapter 4, the level of anxiety provoked by screening for VHD is looked at; this demonstrates that only a small number of patients have significant anxiety levels, but it is more likely in those with a new diagnosis of VHD, and in women.

From Chapter 5 onwards, the thesis focuses on the use of CMR in patients with significant mitral regurgitation (MR). In Chapter 5, the clinical value of quantitative assessment of MR using CMR is examined, showing that it was able to predict progression to symptoms or surgery in these patients.

In conclusion, this thesis offers insights into the prevalence of VHD in the elderly population, and looks at the anxiety associated with looking for VHD in this group. The potential clinical benefits of CMR in patients with MR are examined, and quantification of MR with this modality would appear to be of prognostic utility.

Lay summary

In the modern era, heart valve disease (VHD) in the developed world is mostly related to the ageing process. With an ageing population, the burden of VHD is likely to increase. Despite this, the frequency of VHD, risk factors for developing it, and ways of predicting how it will progress remain poorly understood. Better knowledge of these factors is essential in meeting the challenges of this new "epidemic". The work presented in this thesis aims to improve our understanding of the prevalence of VHD, and the potential benefits of using cardiac magnetic resonance (CMR) assessment of patients with a disease affecting the mitral valve (MR).

The first section of the thesis looks at how frequent VHD is in those aged 65 and over, and looks at factors associated with a diagnosis of VHD. The results from this community-based study in Oxfordshire show a high prevalence of VHD, which is strongly associated with increasing age. The level of anxiety provoked by screening for VHD is examined: only a small number of patients have significant anxiety levels, most commonly in those with a new diagnosis of VHD, and in women.

Next the value of using CMR to assess patients with MR is examined, showing that it is able to predict progression to symptoms or surgery in these patients.

In conclusion, this thesis offers insights into the frequency of VHD in the elderly population, and looks at the anxiety associated with looking for VHD in this group. The potential utility of CMR in patients with MR is examined, and suggests that this test is able to help predict disease progression.

Chapter 1: Introduction

1.1 Background and rationale for the studies

In the late nineteenth and early twentieth centuries, the face of valvular heart disease (VHD) began to change. Until that time, rheumatic fever and its sequela of rheumatic valve disease had been a highly prevalent cause of cardiac morbidity and mortality. Improvements in living conditions led to a decline in this prevalence, which continued with the subsequent introduction and widespread use of penicillin(1-4). Valvular heart disease in modern, developed countries is a very different entity and rheumatic VHD is now rare in Europe(5), but remains common in developing countries(6, 7) and represents a significant public health burden to countries with scarce healthcare resources to tackle it.

Degenerative VHD is now the commonest cause of valve disease in developed countries(5), and is associated with increasing age according to the data available(8, 9). The projected rapid rise in the elderly in the population of developed countries can therefore be expected to result in a parallel increase in the burden of VHD in these countries. Delays in detection or treatment of VHD may result in significant morbidity and mortality, and Davies et al showed that it remains an important cause of heart failure and hospital admission(10). Appropriately timed interventions improve survival, but when treatment is delayed, worse outcomes have been demonstrated(11, 12). Conventional surgical interventions are well established, and newer percutaneous options are gaining an increasing evidence base(13-15).

Despite an awareness that VHD is common, and increases with age, precise contemporaneous epidemiological data are scarce, and there have been no prospective community-based studies of contemporary VHD in the developed world. Lacking such epidemiological data restricts the ability of healthcare planners and economists to plan accurately for the future resources likely to be needed for these conditions.

To date, the majority of studies of the prevalence of VHD have been retrospective, or focussed on aortic valve disease. Although most studies have been population- or community-based, the Euro Heart Survey also provided an insight into VHD seen in secondary care(5).

In the Euro Heart Survey on Valvular Heart Disease, Iung et al looked at contemporary VHD in European patients with respect to their characteristics, management and outcomes; they also assessed adherence to guidelines(5). Looking at 92 centres across 25 European countries, they prospectively gathered data on 5001 patients with native VHD of at least moderate severity, infective endocarditis, or with previous valvular intervention. The commonest valve lesion seen in hospital-based practice was aortic stenosis (AS). Degenerative aetiology accounted for the majority of aortic valve disease and regurgitation; mitral stenosis accounted for just under 10% of native VHD, and was rheumatic in origin in 85%. In the assessment of outcomes and management, the Euro Heart Survey reported that just under one third of patients seen in hospital-based care for symptomatic severe VHD of a single native valve did not have any intervention. The reason for this was often cited as being because the patient's symptoms responded to medical therapy, which is a source of concern. Age was also the commonest “comorbidity” cited by respondents, although was rarely the sole reason for intervention being avoided. Although the Euro Heart Survey data provide excellent insights in to European VHD practice in secondary care, and the modern pattern of VHD seen there, it cannot be used to predict the population prevalence of VHD, particularly primary native VHD. The constraints of a survey such as this preclude in-depth study of individual reasons for lack of intervention, but medical management as an alternative suggests a need for significant education in this area.

Another hospital-based study of VHD looked retrospectively at aortic valve disease(16). Berry et al used a case records identification technique to look at associations with aortic stenosis in particular. They report an iincreased risk of death associated with AS compared with AR or mixed aortic valve disease. Amongst patients with AS, a lower risk of death was seen with female gender, hypertension and the year of admission. Older patients, those of female gender, and those with

comorbidities were less likely to undergo aortic valve replacement. The insights into the under-representation of female patients for aortic valve replacement warrants further investigation, and may be a source of concern. The hospital-based nature of this study however makes it difficult to be sure whether this is applicable to the wider female population with aortic valve disease, or simply those requiring hospital admission for VHD.

Widely regarded as a landmark study of the contemporary prevalence of VHD in the developed world, the study by Nkomo et al looked at the echocardiography of over 28,000 patients, and looked for the prevalence of VHD of at least moderate severity. Data in nearly 12,000 of the echo studies were taken from three large epidemiological studies, which had protocols involving well-defined echocardiographic criteria including thorough valvular assessment. These individuals represent a random population sample. The remainder of the patients were drawn from community-based echo studies within a population with good access to echo. These scans were performed for clinical indications following contact with healthcare professionals. Nkomo demonstrated a striking association between prevalence of VHD and increasing age, with a prevalence of 0.7% in those aged 18-44 years, increasing to 13.2% in those aged ≥75 years in the population-based studies. This association was present in men and women, and in the community-based data. Mitral regurgitation (MR) was the most commonly detected valve lesion in both community- and population-based studies, and mitral stenosis (MS) was the least common lesion. Nkomo's study provides valuable information on the prevalence of VHD, although it relies on retrospective data from a variety of sources. It suggests that in the most elderly segment of the population, there is clinically significant VHD in more than 1 in 10 patients. As discussed further below, this will present an increasing problem as the ageing population expands. The difference in detection rates of VHD between the community-based, clinically indicated studies and the population-based and unselected studies highlights that there is pool of undiagnosed VHD which is not detected in clinical practice. To further assess this, prospective focussed studies would be beneficial. As the study was retrospective and based upon pooled data from other sources, original echo scans were not directly

examined by the investigators. However, the population based studies had well-defined, prospectively determined protocols for echocardiography, which included interrogation of the valves and therefore little in the way of VHD is likely to have been under-diagnosed. In clinically indicated echocardiography, there is the possibility that the severity of VHD might be underestimated if the clinical indication does not suggest VHD as an underlying cause. Echocardiography in the population-based studies was performed between 1989 and 1996, and therefore these data are already over twenty years old; data in the community-based study are also between fifteen and twenty years old. Intervention and imaging in VHD has changed significantly over this period, and updated data are warranted. The ethnic diversity of the participants in these studies is reflective of the diversity seen in the United States (40% black, 59% white, 1% other in the population-based studies; 2.7% black and 90.3% white in the community-based study), but this is not the ethnic diversity seen in the United Kingdom. The population of England & Wales is approximately 95.5% white, 2.6% Asian, and 1.3% Black(17). Although this is closer to the ethnic mix seen within the community-based study than the population-based studies, it is still difficult to be confident that Nkomo's data can be extrapolated to the United Kingdom, and also to a wider European view.

Several large epidemiological studies have analysed their cohorts retrospectively to glean further information on the prevalence and risk factors for VHD. Some have focussed on specific populations, which makes it difficult to extrapolate their data more widely; other have focussed only on aortic valve disease, without assessment of the mitral valve. The Strong Heart Study looked at a range of cardiovascular risk factors, and aimed to ascertain the prevalence and incidence of certain cardiac conditions among thirteen American Indian tribes in the United States. The prevalence of aortic regurgitation, and associated factors, was reported by Lebowitz et al(18). Amongst this selected population, AR was associated with increasing age, aortic root size, the presence of AS and MS, and the absence of diabetes. Jones et al reported on the findings related to mitral regurgitation in the same population(19), and again MR was related to increasing age and presence of MS; in addition lower body mass index, female gender, previous myocardial infarction, and presence of

mitral valve prolapse were also found to correlate with the presence of MR. These data provide a valuable picture of VHD within this specific population, but the lack of diversity amongst study participants means that these results cannot be extrapolated beyond North American Indian populations. The data are also now from scans done twenty years ago, and assuming that the prevalence and clinical correlates are the same now is challenging.

Retrospective studies focussing on aortic valve disease have been published from Norway and Iceland(9, 20). The Tromsø Study looked at a cohort of patients within an original longitudinal epidemiological study from a city in northern Norway(9). The selected cohort underwent echocardiography, including assessment of the aortic valve, and associations, outcomes and progression were assessed. Age was again strongly associated with an increasing prevalence of AS, rising from 0.2% in those aged 50-59 years to 9.8% in these aged 80-89. The investigators also demonstrated a mean rate of progression of AS of 3.2mmHg per year. Asymptomatic AS and aortic valve replacement were not found to be associated with increased mortality compared to the general population. As well as only focussing on AS, a further limitation to this study is that data from hospital-based echo studies were included in the analysis, alongside the data from study participants. These hospital-based studies were done in response to a clinical indication, which is likely to introduce bias in to the results.

The AGES-Reykjavik study data presented by Danielsen et al also looked at AS, without considering other valve lesions(20). The original AGES-Reykjavik study was not aimed specifically at VHD, but echocardiographic and cardiac computed tomography (CT) data were obtained in a subset of participants. The use of echocardiographic data demonstrated that among those aged ≥80 yrs, the prevalence of severe AS was 7.3%, and the authors highlighted the potential for VHD to become a significant problem associated with an ageing population. The lack of specificity for valve assessment in the study cohort means that the prevalence of AS may have been prone to a minor underestimate. The long follow up time of participants in this study cohort may provide useful extra information on progression and outcomes. The investigators also calculated a calcium score on cardiac CT which they found to be

equivalent to severe AS on echocardiography. With the increasing use of cardiac CT in routine clinical practice, this may assist in the detection of significant VHD in the wider patient population.

There have been a variety of studies looking at various aspects of VHD. Some have looked at hospital-based care of VHD, others have looked at specific ethnic populations or individual valve lesions; most are retrospective. OxVALVE PCS is the only contemporary, prospective screening study aimed specifically at the detection of VHD in the developed world.

Current practice for the management of VHD is based on guidelines which rely heavily on consensus of opinion(21-23), and include data from studies which may now be outdated. Newer data would perhaps suggest that more proactive approaches to the intervention may be appropriate, especially in the most severe forms of VHD(24, 25), but further evaluation of this is required, and is being actively encouraged by national societies(26).

In order to optimise the delivery of care to patients with valvular heart disease, a clearer understanding of the population affected is required, alongside expert follow-up and imaging services, armed with a toolkit for accurate risk stratification. At present there are many areas of valvular heart disease where the management is unclear or a source of debate. How big is the problem of valve disease at present, and how many might it affect in future? Which patients need to be followed up, and who might be safely be left alone? Are there any options for slowing disease progression? When should truly asymptomatic patients with severe VHD have surgery? This thesis aims to provide some insights into aspects of these unanswered questions, including providing an insight into the contemporary epidemiology of VHD in the elderly population, thus helping to define the size of the problem. It also looks at the contribution of cardiac magnetic resonance imaging in the quantification of primary mitral regurgitation, and how this might assist with risk-stratification in this group.

1.2 Defining the size of the problem

According to the data available, the prevalence of VHD increases dramatically above the age of 65, with an estimated prevalence of 0.9% in those aged 18-64 and 9.9% in those ≥65 years of age(8). These data are based on pooled data from population-based studies, undertaken over a quarter of a century ago, and which were not undertaken specifically to look for valvular heart disease. The proportion of the population aged over 65 is increasing across the developed world. Over the last decade, the proportion of the population in this age group has increased by an average of 1.9% in the countries of the European Union (EU)(27). This increase in the elderly section of the population is predicted to continue, and will bring with it many challenges for healthcare resource planning. Figures 1.1 and 1.2 show the change in the EU population between 2001-2013, and the predicted change in the population age structure in the future. The increase in longevity of our population is anticipated to be accompanied by an increase in age related conditions, among them valvular heart disease as highlighted by a recent editorial(28). Appropriate planning and adequate resource allocation to deal with this increase will only be possible with an up-to-date epidemiological picture. Epidemiological studies of VHD may also allow the identification of groups of patients with well-defined VHD of all severities. These groups may be suitable for studies of progression, medical therapies, novel biomarkers, or different surgical interventions.

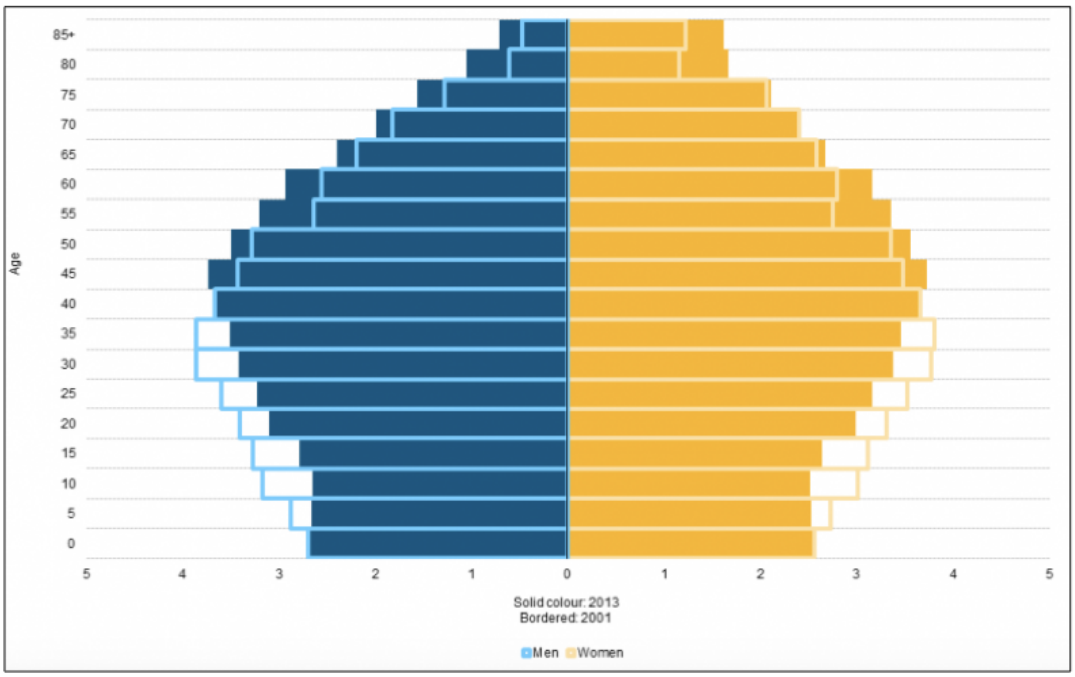

Figure 1.1 EU population pyramid showing the change in each age group from 2001 to 2013. (From Eurostat)

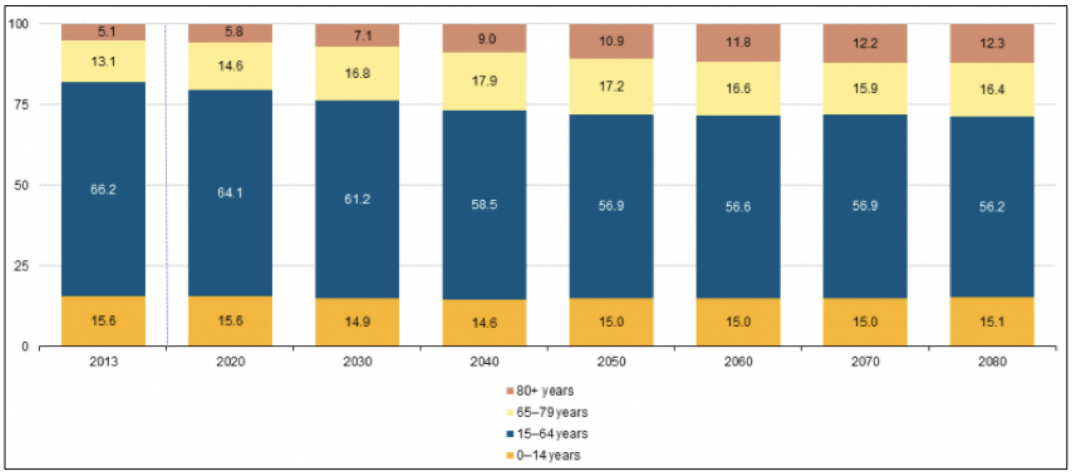

Figure 1.2 EU population age structure 2013-2080 (From Eurostat)

1.3 Echocardiography for the detection of VHD

The data from the United States (US), published by Nkomo et al(8), highlight the difference in the detection rate of VHD when echocardiography is performed with clinical indications, and that estimated from population-based studies (1.8% vs 2.5%). Clinical auscultation for valve disease has the benefit of being low-cost, easily accessible and non-invasive. It can be used opportunistically for the detection of cardiac murmurs, and VHD may be an incidental finding during examination for an unrelated issue. However, auscultation is well-recognised as having a limited sensitivity for the detection of VHD(29, 30) and should not be relied upon to uncover all valve disease. The level of proficiency in auscultation amongst primary care doctors is reportedly as low as 40%(31, 32). This is a source of concern in a condition in which symptoms occur late and are a harbinger of adverse outcomes, and which currently requires opportunistic detection to prompt further investigation and ongoing surveillance. Transthoracic echocardiography (TTE) is known to maximise the detection of valvular heart disease(6, 8), and has well-established national and international guidelines(33-35). It is safe, portable, non-invasive, reproducible, cost-effective, and widely available. It does not rely on doctors to perform it, but can be expertly carried out by appropriately trained and experienced physiologists. A single comprehensive study can permit assessment of valve

morphology, severity of valve disease, and the effect on the ventricle. These features all make it an ideal tool for screening studies for VHD, investigating a newly-detected murmur, and for longitudinal follow up of those with established VHD.

Current detection of VHD relies heavily on clinical auscultation, which has its deficiencies as already described, and also on incidental detection of VHD when echocardiography is performed for reasons other than murmurs. Despite published criteria for the use of echocardiography, echocardiography may not be fully utilised in the detection of VHD(36). Deficiencies in the reliance on auscultation and appropriate echo use are likely to contribute to the significant number so patients in the United Kingdom who undergo valve surgery with NYHA class III or IV symptoms(37). The awareness of VHD amongst patients is also low, according to a recent survey reported by a British Heart Valve charity(38). This lack of awareness may contribute to the late presentation to health services with symptom onset.

The utility of routine echocardiographic screening for VHD would require significant investment in resources and personnel. The potential cost benefits of such an intervention would require in-depth analysis of the costs of screening and the anticipated savings and benefits which it might produce; such an assessment was not the intention of the work presented in this thesis, and this is therefore not assessed. Indiscriminate population screening may also risk turning healthy people into patients, as well as providing inappropriate false reassurance(39, 40). Any potential screening programme should target those at the highest risk, including older patients, those with hypertension, coronary disease, dyslipidaemia or renal dysfunction(9, 41, 42). The British Heart Valve Society have even suggested that hand-held echocardiography may be useful when access to full echo services is challenging(43). They suggest that hand-held echo could be used as a filter to determine which patients require full echocardiography. This approach may avoid over-stretching busy echo departments with well people.

In due course, it may be possible to risk stratify people individually through a combination of clinical risk factors, serum biomarkers and even genetic screening. Until such time as this becomes a reality, all clinicians need to have a high index of

suspicion of VHD in patients with risk factors, examine them thoroughly when the opportunity presents, and refer for echo when appropriate.

The first part of this thesis describes the development, methods and results of the OxVALVE Population Cohort Study (OxVALVE PCS). This prospective, community-based, echocardiographic screening study in the Oxfordshire population aged 65 years and older aims to shed light on the present-day epidemiology of VHD in a developed country. Detailed demographics and medical histories are captured, allowing the possibility of risk factor profiles for VHD to be established. By setting a low threshold for a positive screen, patients with milder forms of VHD are captured, who may be suitable for future studies aiming to elucidate the pathophysiology and natural history of different forms of VHD. Those identified as having more advanced VHD may be suitable for inclusion in other ethically approved studies, which may perhaps be interventional - medical, surgical or percutaneous - or imaging-based. Participants in OxVALVE PCS also provide blood samples, which can be used for DNA analysis, as well as for the measurement of biomarkers. Genetic analysis may allow markers of increased risk, or of more rapid progression, to be identified and studied, while testing for biomarkers may be for those molecules already identified as potentially useful in VHD(44-47), or those identified in the future.

Thus OxVALVE PCS may lead to an improved understanding of the epidemiology of VHD in the most at-risk section of the population, allowing better healthcare planning, and the evolution of structured screening, surveillance and referral protocols in those identified as having VHD. Increased awareness of the risk and appropriate management of VHD among primary care clinicians may be another consequence of involvement in screening.

1.4 Pathogenesis, pathophysiology and natural history of valvular heart disease

The mechanisms involved in the development and effects of valvular heart disease as a whole remain poorly understood compared with other areas of cardiovascular medicine. Although the mechanisms underlying the development and progression of

aortic stenosis have become better elucidated in recent years, those underlying aortic and mitral regurgitation are less well defined; the relative rarity of mitral stenosis in the developed world also means that many aspects of this are particularly challenging to study. The natural history and factors affecting progression differs between individuals, as well as between lesions. Improvements in understanding in these areas may lead to the development of efficacious medical intervention, improved risk stratification and more streamlined approaches to surveillance with timely surgical intervention as a result. As the most common clinically significant forms of VHD are those affecting the aortic and mitral valves(5, 8), the discussion on pathogenesis and pathophysiology of VHD below is restricted to these valves.

1.4.1 Aortic stenosis

1.4.1.1 Pathogenesis and pathophysiology of aortic stenosis

Aortic stenosis (AS) is the commonest valve lesion seen in clinical practice(5, 41), and affects around 2% of the population in those aged over 65(42). Aortic stenosis is characterised by thickening and stiffening of the valve leaflets, resulting in progressive narrowing of the valve, with a resulting increase in after load on the left ventricle. Calcific aortic stenosis is the commonest cause in developed countries, although rheumatic and congenital AS are also seen in a small proportion of cases. Bicuspid aortic valves (BAV) are also affected by AS, in a similar way to tricuspid aortic valves. The markedly abnormal mechanical stresses to which the valve is exposed result in more accelerated stenosis. Rarer causes of AS are seen in association with conditions such as hyperparathyroidism, Paget's disease and systemic lupus erythematosus.

Calcific aortic stenosis is no longer viewed as simply a process of "wear and tear" on the valve, although the term "degenerative" AS is still frequently used. Similar mechanisms to those involved in the development of atherosclerosis have been implicated in the development of calcific AS. Epidemiological studies have demonstrated common risk factors for AS and atherosclerosis(42, 48, 49), and

histological studies have also supported this. However, up to half of those with calcific AS do not have clinically significant atherosclerosis(50). Damage to the endothelium of the aortic valve as a result of mechanical stress leads to infiltration of the valve with inflammatory cells and lipids. Lesions seen in the early stages of aortic valve disease have been shown to contain the same lipids as seen in atherosclerosis (such as low-density lipoprotein and lipoprotein (a))(51, 52). The presence of these within the valve stimulate an inflammatory reaction, with the release of cytokines and infiltration with inflammatory cells(53-55). The role of inflammation in the development and progression of aortic stenosis is also supported by the finding of increased levels of C-reactive protein in patients with AS(56), and the finding of increased 18F-sodium fluoride (18F-NaF) and 18F-fluorodeoxyglucose (18F-FDG) levels on positron emission tomography. Dweck et al showed that levels of both 18F-NaF and 18F-FDG were increased in patients with AS when compared with levels in controls(57). They also demonstrated an increase in uptake of both tracers correlating with increasing severity of AS, although this correlation was stronger for 18F-NaF than 18F-FDG.

Subsequent fibrosis and calcification resulting from the inflammatory process give rise to progressive thickening of the valve. Myofibroblasts and other inflammatory cells in the valve leaflets secrete matrix metalloproteinases, leading on to remodelling of the leaflet matrix(55, 58). The process of fibrosis in the aortic valve also involves the renin-angiotensin system, and angiotensin-converting enzyme (ACE) has been shown to be present in stenotic aortic valves, but not in controls(59). The potential for altering outcomes in AS by targeting the renin-angiotensin system has therefore become a focus of recent studies(60, 61).

Calcification of the aortic valve can be seen from the early stages of AS, and progression from aortic sclerosis may be due to the acceleration of this process as myofibroblasts differentiate into osteoblasts. Valvular calcification is well demonstrated by computed tomography, which can be used to quantify the degree of calcification(62, 63). The severity of this calcification has been shown to correlate with disease progression and outcomes, as well as with severity of AS(64-66). The presence of these osteoblasts leads on to more advanced calcification, and Mohler et

al have demonstrated the presence of bone formation and remodelling in end-stage AS(67).

Although AS and atherosclerosis share a variety of risk factors, they do not always co-exist. The failure of drug interventions used in atherosclerosis to have beneficial effects in AS suggests that the pathophysiological processes involved diverge. The increasing severity of valvular stenosis, which is related to the degree of calcification of the valve, is what drives outcomes in AS, rather than underlying inflammation itself.

Aortic stenosis is not just a disease affecting the aortic valve, but the effects of AS on the left ventricle (LV) are of pivotal importance also. Although declining left ventricular function is an indication for consideration of surgery in those with severe aortic stenosis according to current guidelines(21, 68), a reduction in left ventricular ejection fraction is only seen late in the disease and is associated with a poor prognosis(69). Recent studies have suggested that the response of the myocardium to AS, including changes in the geometry of the LV, LV strain, and fibrosis, may be important in the prognosis of patients with asymptomatic aortic stenosis(70-72).

As AS progresses, the valve becomes increasingly stiff with a decreasing valve area. This results in an increasing pressure gradient across the aortic valve, reflecting the greater pressure required from the LV in order to maintain blood flow across the valve; this leads to progressive hypertrophy of the LV. The development of left ventricular hypertrophy (LVH) helps to normalise afterload, and it might be expected that the degree of LVH would correlate with severity of AS. However the degree of left ventricular hypertrophy does not correlate well with stenosis severity(73-75). Certain groups of patients, most notably elderly women, appear to have greater degrees of LVH than is needed in order to normalise wall stress(76). Concentric LVH has also been shown to lead to abnormal coronary blood flow(77, 78). More recently evidence has suggested that more extreme degrees of LVH may be maladaptive and associated with poorer outcomes. In the Simvastatin and Ezetimibe in Aortic Stenosis study, Rossebo et al showed LVH on echocardiography to be associated with poor prognosis(79). LVH in asymptomatic patients with AS is an

independent risk factor for cardiovascular events(80), and in those undergoing aortic valve replacement it is associated with an adverse prognosis(81, 82). Conversely, Kupari et al found that those patients with AS who had concentric remodelling but no LVH were likely to have the best outcomes(74).

Left ventricular remodelling response to pressure overload involves a variety of complex factors, including genetic factors, co-morbidities and gender(83-86). Gene polymorphisms encoding for ACE have been shown to influence both hypertrophy in response to AS, and remodelling following aortic valve replacement(83, 87). Greater wall thickness and smaller LV cavity size have been demonstrated in females with AS when compared to males(88), but following valve replacement hypertrophy regresses faster in women(85). In the presence of metabolic syndrome and diabetes, more pronounced LVH has also been shown(84, 86).

Alongside the process of left ventricular hypertrophy, a reactive diffuse interstitial fibrosis occurs in patients with AS(89). The mechanisms which drive this process involve numerous complex mechanisms. Several of these are common to the processes involved in fibrosis occurring within the aortic valve. Increased pressure in the LV, such as is seen in AS, leads to local cell damage(90), and chemokines such as transforming growth factor beta (TGFβ), matrix metalloproteinases (MMPs) and angiotensin II are released. This attracts inflammatory cells into the extracellular matrix, which then bind to integrin(91). Pathways involving TGFβ and angiotensin II lead to increases in collagen I and III(92).

Diffuse myocardial fibrosis can be quantified by biopsy, but this is an invasive procedure and may be subject to sampling error. Non-invasive assessment of myocardial fibrosis can be undertaken using late gadolinium enhancement techniques on cardiac magnetic resonance imaging, tending to show a pattern of midwall fibrosis in patients with AS. Midwall fibrosis has been shown to be an independent predictor of mortality(71, 93). This adverse prognosis is likely to be due to adverse remodelling of the ventricle, poorer LV function, as well as arrhythmia.

The pathogenesis and progression of AS are complex processes. AS shares risk factors with atherosclerosis, but once inflammation has been established, calcification of the valve supervenes leading to progressive narrowin(94)g and increased LV afterload. The response of the LV to the increased afterload may be maladaptive, leading to excessive hypertrophy associated with fibrosis. The rate of progression of AS and LV adaptation vary, and complex pathways are involved.

1.4.1.2 Natural history of aortic stenosis

The development and progression of AS occurs over a long timespan(69, 95), although the rate of progression is highly variable. In patients with sclerotic aortic valves only a minority will progress to haemodynamically significant stenosis in a five year period(96, 97). The development of stenosis is present, the severity progresses in nearly all patients, resulting in many requiring intervention on the valve(98, 99). Otto et al followed 123 patients prospectively and found an average increase in the mean transvalvular gradient of 3-10mmHg per year, 0.1-0.3m/s increase in the peak velocity across the valve, and an average fall in valve area of $0.1cm^2$ per year(98); rate of progression was associated with transvalvular jet velocity at baseline, rate of change of jet velocity and patients' functional status. Other factors associated with more rapid progression of AS include age, gender, renal dysfunction and hyperlipidaemia(100), calcification of the valve as measured by cardiac CT(101, 102), and also sodium fluoride uptake on PET-CT(103, 104).

The rate of symptom onset is also highly variable. Risk factors for symptom onset are similar to those associated with more rapid progression of AS, including gender, age, severity of stenosis and functional status. Jet velocity is strongly predictive of rate of symptom onset: those with a jet velocity below 3.0m/s have the lowest rates of symptom onset, and those with a jet velocity over 4.0m/s having the highest rates(98). Those with severe disease may remain symptom-free for some time, but those most at risk progressing to symptoms include those with more calcified valves, and those aged over 50 years(65, 105). When AS becomes very severe (maximum velocity greater than 5.0m/s), the rate of symptom onset is sufficiently high that

consideration may be given to valve replacement before symptoms are reported(25, 106).

The commonest symptom seen in severe aortic stenosis is decreased exercise capacity due to breathlessness(98). This may be difficult to detect if patients subconsciously limit their activities in order to avoid provoking their symptoms. The onset of angina is a common symptom of severe AS, even in the absence of coronary disease, and Horstkotte et al found a mean survival of 45±13 months after the onset of angina; mean survival with syncope and heart failure was 27±15 months and 11±10months respectively(107).

1.4.2 Aortic regurgitation

Aortic regurgitation (AR) is less common than aortic stenosis, and accounts for approximately 10% of VHD seen in the hospital setting(5), and the majority of AR is chronic. Chronic AR may result from primary abnormalities of the valve with leaflet prolapse or malformation, myxomatous degeneration of the valve, and as a result of a bicuspid aortic valve. It may also be secondary to dilatation of the ascending aorta, with annular dilatation and failure of leaflet coaptation. Aortic dilatation may be due to hypertension, or Marfan's syndrome and other connective tissue disorders, such as Ehlers-Danlos syndrome or osteogenesis imperfecta. Thickening and retraction of the leaflets of the aortic valve may be seen following rheumatic fever, resulting in central aortic regurgitation, but this is a rare cause of AR in developed countries. Aortitis due to ankylosing spondylitis, rheumatoid arthritis, giant cell arteritis, or syphilis (now rare) may result in AR. However, in up to a third of cases of pure AR, the aetiology has been described as unclear in a pathological study examining valves excised at surgery(108).

Acute AR is much less common than chronic AR, and is associated with traumatic injuries to the aortic valve and aorta, or aortic dissection involving the aortic root and valve. It may also complicate infectious endocarditis, with leaflet tearing or when perivalvular abscess results in a communication between the aortic root and LV.

As with aortic stenosis, the effect on the left ventricle is of great importance in how the lesion is tolerated. Studies suggest that over time the regurgitant orifice area increases in size, resulting in increased volume and pressure loads on the LV(109). In chronic AR, compensatory mechanisms of the LV initially maintain cardiac performance. These mechanisms include increases in end-diastolic volume, an increase in LV compliance, and both eccentric and concentric hypertrophy. An increase in total stroke volume is required, in order to eject forward stroke volume in addition to regurgitant volume. The degree to which total stroke volume is increased is dependent on the severity of the AR, and it has been shown that the greatest increases in LV mass and volumes occur in those with more severe AR(110). Increasing LV dilatation provides a greater diastolic volume, thus permitting a larger total stroke volume. This is achieved by rearrangement of myocardial fibres, and the addition of new sarcomeres and subsequent eccentric hypertrophy(111). Increasing chamber size is associated with increasing systolic wall stress, resulting in further hypertrophy(112), and so increasing LV volumes are associated with increasing LV mass. With increasing disease progression, normal ejection fraction is maintained, in spite of increased afterload, by compensatory hypertrophy and recruitment of preload reserve(113-115). This balance cannot be maintained indefinitely, and a decline in LV function occurs. The point at which this occurs is difficult to define, and cannot be precisely identified by a single measurement at present.

In the setting of acute AR, these compensatory mechanisms do not have the time to take place. The effect on the left ventricle is therefore much more abrupt. Left ventricular end diastolic pressure increases rapidly, and pulmonary oedema ensues. Severe acute AR results in a rapid fall in cardiac output, and cardiogenic shock may develop. In order to try and compensate for the drop in cardiac output, a tachycardia develops. Lower myocardial perfusion pressure due to severe acute AR, in combination with increased cardiac work, leads to myocardial ischaemia, and a further decline in cardiac function(116). A downward cycle of dysfunction sets in, unless rapid intervention to correct the regurgitation can be undertaken.

1.4.3 Mitral regurgitation

Mitral regurgitation (MR) is the most commonly detected form of valve disease in developed countries(8), and is the second commonest lesion requiring intervention(5). It can be either primary MR, due to processes such as myxomatous degeneration, or secondary to pathology affecting the muscle of the left ventricle, such as ischaemia or underlying cardiomyopathy. Infective endocarditis is also an important cause of MR(5, 117). The natural history of secondary MR relates to the underlying cause, and best approaches to its management remain a source of debate.

Although degenerative MR can result from mitral annular calcification in a few cases, the commonest cause of chronic, isolated MR is mitral valve prolapse (MVP)(118, 119). MVP is defined as prolapse of 2mm or more, of either or both leaflets of the mitral valve, above the valve annulus as seen in the parasternal long axis and other views(21). Using this definition, the prevalence of MVP is between 2-3%, with an equal gender distribution(120). Milder degrees of MVP may occur without significant regurgitation if coaptation of the leaflets is maintained. Moderate MVP is considered to be that when the leaflet tips remain in the left ventricle, and the body of the leaflets “billow" into the left atrium (LA). In severe MVP, the leaflet tip everts completely into the LA; this is often associated with rupture of one or more of the chordae tendinae. MVP is multifactorial, resulting from various connective tissue disorders such as Marfan syndrome, Ehlers-Dalos and pseudoxanthoma elasticum; differences in the geometry of valve and ventricle, such as excess leaflet tissue, excessive chordal extension, or small LV cavity size; or in association with histological changes within the valve tissue, known as myxomatous degeneration, which result in leaflet thickening and redundancy.

The normal tissue of the mitral valve leaflets consists of three layers: the atrialis layer is a layer of collagen and elastic tissue, which forms the atrial surface of the valve leaflet; the middle layer is termed the spongiosa layer, which is composed of structural proteins and proteoglycans; and the ventricularis or fibrosa layer on the ventricular aspect of the valve, which is predominantly formed of collagen.

Myxomatous degeneration involves changes predominantly to the spongiosa and fibrosa. The spongiosa layer has been shown to contain increased numbers of interstitial cells. These cells have the properties of activated myofibroblasts, and also have increased concentrations of proteolytic enzymes such as matrix metalloproteinases, which result in the degradation of elastin and collagen(121, 122). Increased proteoglycans and glycosaminoglycans have also been shown to extend into the fibrosa and chordae(123). These higher concentrations of proteoglycans within the fibrosa are thought to affect the tensile strength of the valve tissue. This may be due to dysfunction of the interaction between collagen fibres and proteoglycans(124). Changes have also been described to the structure of collagen in all three layers of the valve leaflet, with a more diffuse and disorganised pastern of distribution of elastin, collagen I and collagen III, compared with normal valve structure(122, 125).

Although some of the mechanisms involved in myxomatous degeneration and MVP have been elucidated, triggers for the onset of these remain unclear. As with the changes in AS, it has been suggested that exposure of an abnormal valve to repeated mechanical stress may be involved in the onset of the pathological process(126). Genetics also seem to play a part, although the majority of cases of MVP appear to be sporadic. This genetic association was described over forty years ago(127, 128), with an autosomal dominant pattern of inheritance. However, the penetrance is variable, and the clinical presentation shows marked variation. Although two genes associated with this pattern of inherited myxomatous mitral valve prolapse, MMVP1 and MMVP2, have been identified and mapped to specific loci(129, 130), the proteins coded for by these genes remain unidentified. Although polymorphisms associated with MVP have been identified, these do not necessarily correlate with the degree of severity of MVP. Nasuti et al demonstrated abnormalities in the distribution and structure of proteins such as fibrillin, elastin and collagens I and III in patients with MVP(131). This gives rise to the possibility that the defect may not lie with the proteins themselves, but may be post-translational. Environmental factors, as well as age, may affect the penetrance of genetic defects involved in the development of MVP, a suggestion supported by data showing that MVP is not seen

on echocardiography of newborns(132). MVP is associated with several inherited connective tissue disorders. Specific genetic defects in these disorders may give rise to a higher prevalence of MVP within these populations. In type IV Ehlers-Danlos for example, the production of collagen III is abnormal, and these patients may have a higher prevalence of MVP than in other types of Ehlers-Danlos(133). A polymorphism in the gene coding for collagen III which has been linked to MVP in a group of Taiwanese patients is also located in the region of the known gene mutations involved in type IV Ehlers-Danlos syndrome(134).

Mitral regurgitation associated with infective endocarditis may be the result of perforation of the valve leaflets, or to chordal rupture, due to the destruction associated with the infection. Endocarditis may occur on a valve already known to be abnormal, and MVP with MR is thought to be associated with it due to the presence of thickened valvular tissue and turbulent flow across the valve. Data suggest an increased risk of between three- and eightfold for patients with MVP and MR, resulting in an annual incidence estimated to be approximately 0.02%(135-137), although these data are from three decades ago. Various risk factors have been suggested for the development of endocarditis in those with known MVP, including gender, age, leaflet thickening and redundancy, and the presence of a systolic murmur(136-140).

Mitral regurgitation results in an increased volume load on the left ventricle, leading to the initiation of compensatory mechanisms of the heart and circulation. In acute MR, such as may occur with a flail leaflet or chordal rupture, there is a sudden increase in volume load in the left atrium and ventricle. This sudden loading on the LA results in back pressure on the pulmonary vasculature, with subsequent pulmonary congestion. Cardiac output also falls due to the decrease in forward stroke volume. Volume overloading of the LV is countered by the Starling mechanism, and fractional shortening increases, with decreased LV end-systolic volume due to regurgitation into the LA. In response to the decreased cardiac output, a compensatory tachycardia occurs. If these mechanisms are not able to compensate adequately for the severe acute regurgitation, or if interventions are not promptly instituted, cardiogenic shock and pulmonary oedema result.

In order to adapt to chronic mitral regurgitation, left atrial dilatation occurs with increased compliance, and a decrease in LA pressure can be seen. Left ventricular dilatation also occurs, due to the addition and rearrangement of sarcomeres(141, 142), allowing normalisation of the preload on individual sarcomeres. A greater LV volume can also be sustained in the presence of normal LV diastolic pressures, and systolic wall stress can be restored to normal levels(143-146). LV ejection fraction may be normal or high in chronic, compensated MR as a result of these adaptive processes, despite the altered left ventricular function(147). In fact, when LV ejection fraction is borderline, it is likely to reflect underlying systolic dysfunction in this context(148, 149). In the presence of chronic MR, increasing severity of regurgitation, along with increasing chamber dilatation, eventually progresses to a decompensated stage. Increasing LV dimensions themselves can further impair leaflet coaptation, resulting in greater degrees of regurgitation and volume overload. The ventricle becomes more globular in shape, resulting in greater systolic wall stress(145, 150, 151).

1.4.4 Mitral stenosis

Mitral stenosis (MS) is the least frequent left-sided valve lesion, and is most frequently a consequence of previous rheumatic fever(5). The incidence and prevalence of rheumatic fever has wide geographical variation, and consequently the morbidity and mortality of MS differs between developed and less developed countries(6, 152). Many of the studies of MS are very dated, reflecting the decrease in prevalence in the developed world over recent decades.

Rheumatic fever follows infection with Group B haemolytic streptococci in 2-3% of patients. Pancarditis results from autoimmune activation involving the M protein antigen common to both the heart and the bacterium. A chronic inflammatory process results in the valve, with subsequent fibrosis. Progressive commissural fusion results in a fixed mitral orifice. Thickened and restricted valve leaflets, and fibrosis and calcification of the subvalvar apparatus also contribute to progressive stenosis.

The natural history of rheumatic MS is difficult to elucidate, as the diagnosis of rheumatic fever may be missed, especially in the less mature healthcare systems in countries in which it is most prevalent. This is well illustrated by the work of Marijon et al, who demonstrated a ten-fold increase in detection rates of rheumatic valve disease using a systematic echocardiographic programme compared to estimates relying purely on clinical data(153). Studies looking at the progression of MS are are all small and retrospective, with a heterogeneous mix of those who progressed slowly and those whose valve area decreased more rapidly. Rheumatic fever is also often recurrent. Chronic rheumatic valve disease occurs in the majority of patients following their first episode of carditis. Meira et al identified potential predictors for developing progressive rheumatic valve disease; these included the severity of the carditis, low educational level of the patient's mother, and recurrent rheumatic fever(154).

Other causes of haemodynamically significant MS are rare. Elderly patients may have degenerative calcification of the mitral valve annulus, but this only rarely leads to significant MS. In such cases where MS does result, it is calcification and restriction of the leaflets which is the main process, rather than commissural fusion. Conditions associated with chronic inflammation (such as systemic lupus erythematosus), carcinoid syndrome, and certain drugs (for example methysergide and fenfluramine-phentolamine) may also cause mitral stenosis. All of these aetiologies result in predominantly leaflet involvement, with thickening and restriction, rather than fusion of the commissures. Congenital causes of MS are extremely rare, and tend to involve abnormalities of the subvalvar apparatus.

The progression of MS leads to an increasing diastolic pressure gradient across the mitral valve. This is dependent on mitral valve area, but is also related to heart rate and flow across the valve. Trans-valvular flow increases during atrial contraction, and this results in an increase in the trans-mitral gradient during this phase of the cardiac cycle. However, the onset of atrial fibrillation in the setting of severe MS may result in a paradoxical decrease in trans-valvular gradient as the contribution of atrial contraction is lost. Atrial fibrillation is common in more advanced MS as the high pressure gradient across the valve results in an increase in left atrial pressure.

This elevated left atrial pressure leads to dilatation of the left atrium, which in turn predisposes to the development of atrial fibrillation; the onset of AF has been associated with increased mortality in this context(155). The impaired trans-atrial flow due to MS, coupled with the stasis seen with AF, is associated with left atrial thrombus formation. The commonest site for thrombi to form is in the left atrial appendage(156).

The left ventricle in MS does not dilate or hypertrophy, but diastolic filling is impaired. As a result, the contribution of LV filling due to atrial contraction is more significant than normal. This reliance on active LV filling is why the onset of AF may result in a sudden worsening of symptoms.

Following on from the increasing LA pressure, pulmonary artery pressure increases. Early changes in the arteries and arterioles involve medial thickening, followed by thickening of the intima(157). These changes are thought to be reversible if pulmonary pressures decrease, but if not, progression to irreversible changes can be seen. These changes include fibrin deposition and infiltration of inflammatory cells in the vessel walls, and ultimately the development of plexiform lesions with end-stage pulmonary hypertension. In response to increasing pulmonary hypertension, the right ventricle hypertrophies and dilates, and will eventually fail. However, the degree of right ventricular failure in patients with MS does not correlate well(158).

Asymptomatic patients are report as having an 80% survival at 20 years, although one study found a rate of progression to symptoms of 50% by 10 years(159). The onset of symptoms associated with MS denotes a poor prognosis. In those patients who decline intervention, Horstkotte et al found survival rates of only 44% at five years(160). Mortality in MS is most commonly due to heart failure or thromboembolic complications(161).

1.5 Mild valvular heart disease.

The detection of mild valvular heart disease, in particular mild regurgitation, is associated with a benign prognosis. European guidelines suggest longer intervals between follow up of these patients, and mild mitral regurgitation is not mentioned as requiring serial testing(162). However, the study of mild forms of valve disease have a number of benefits.

Early changes in the valve itself may reflect how the valve lesion evolves over time, and whether it progresses to clinical significance. The changes seen in aortic sclerosis for example with the deposition of lipoproteins, inflammatory cell infiltrates and microscopic calcification, may or may not progress over time to the more florid changes seen in aortic stenosis. The reasons why some individuals develop progressive AS, while others do not, are unclear. The identification of risk factors for progression may provide potential targets for intervention, and highlight those individuals who would benefit most from ongoing surveillance.

The natural history of all forms of valve disease is poorly understood, increasing the challenge of follow up and timing of intervention. The assumption that milder forms of VHD have benign outcomes may provide a false degree of reassurance for clinicians and patients. Even in mild and moderate disease there is evidence to suggest that survival is adversely affected(99). Progression of aortic sclerosis to stenosis was shown in 16% of patients within 7 years(163). Milder forms of VHD cannot therefore be assumed to be inconsequential. Providing information to patients about whether they might expect their VHD to require intervention in due course, and within what timescale, is challenging with the current gaps in knowledge in this area. The longitudinal study of cohorts of those with mild valve disease may provide further insights into this aspect of VHD. An improved understanding of the natural history of VHD may also allow improved surveillance schedules, assisting with the rationalisation of healthcare resources.

Medical therapies which reliably retard the progress of VHD remain elusive. Although the use of statins in AS providing a period of optimism that they would prove efficacious, this has thus far not proven to be the case. Therapeutic intervention in the earliest forms of VHD may be required if treatment is to affect the pathologic mechanisms before irreversible and progressive changes occur. As patients with mild VHD may not be seen in routine clinical practice, their inclusion in screening studies may provide a resource for future research.

The inclusion of participants with mild VHD, including aortic sclerosis, within the OxVALVE PCS study will allow the identification of cohorts with the different valve lesions for future study. These studies may be interventional, imaging based, genetic or looking at other biomarkers of disease.

1.6 Impact and attitudes to screening

Although screening programmes may play a vital role in the detection and management of certain conditions, there have been concerns raised about the potential for anxiety to be provoked by such programmes(164, 165). Various studies have been undertaken in order to determine whether there is good evidence for this, but have concluded that this is not the case(166). Cardiovascular disease is one of the major areas where screening interventions have been employed, and specific studies have been undertaken to assess the psychological impact of these, which have reassuringly demonstrated no significant adverse psychological or emotional impacts(167-169). Valve disease has a less prominent position in the public consciousness than many other conditions with well-established screening programmes, and the use of echocardiography is unfamiliar to many. An assessment of whether or not anxiety might be provoked by actively looking for VHD is therefore an important step to avoid potentially adverse psychological and emotional outcomes.

Screening tests need to be acceptable to the target population in order to achieve sufficient coverage. If the uptake of screening is too low, it ceases to be cost

effective, as well as ineffective. Any screening programme for VHD therefore also needs to be acceptable to those at whom it is aimed.

As an important part of OxVALVE PCS, a questionnaire aimed at assessing the levels of anxiety triggered by participation was included. Participants also completed a questionnaire to capture attitudes to screening for VHD, as well as how acceptable the use of TTE was to this group. The data presented in this thesis also demonstrates not only the feasibility of a large-scale screening programme for VHD, but that the target population find it an acceptable test, and are not unduly anxious about undergoing it.

1.7 Assessment of mitral regurgitation

Mitral regurgitation is the second most frequently detected form of valve disease in OxVALVE PCS, after aortic sclerosis. Indications for intervention in this group rely on the accurate and reproducible assessment of the mitral valve and the left ventricle. This is most commonly done by TTE, although this method has significant drawbacks, and identification of patients at highest risk for requiring intervention are not well defined. This area needs further study, and the second part of this thesis includes work in this area.

1.7.1 Trans-thoracic echocardiography

Current guidelines for the echocardiographic assessment of mitral regurgitation (MR) severity recommend an integrated approach, using quantitative and supportive features(33, 170). The use of qualitative assessment alone has a variety of potential sources of error, including sensitivity to machine settings, eccentricity of jets, and variability according to loading conditions. Quantitation has been linked to outcomes(12, 171), but relies on precision and reproducibility. Although there is evidence of consistency within single centres(172, 173), this is not necessarily the case between centres(174). As with all echocardiographic assessments, adequate

image quality is vital. This may be prohibited by inadequate acoustic windows, co-existent respiratory disease, previous thoracic surgery or unfavourable body habitus.

Recommendations for the evaluation of regurgitant valve disease include an assessment of the overall valve structure and impact of regurgitation on the chambers of the heart by TTE. This includes looking for flail leaflets or ruptured chordae, valvular calcification or vegetations. The presence of any of these may support an assessment of severity of regurgitation, and may also inform clinical decision making about the acuteness and impact of a lesion. The anatomy of the mitral valve will also influence its suitability for surgical repair. A full assessment of the anatomy may require trans-oesophageal echo, but TTE may also provide information on this. The assessment of ventricular size and systolic function is not specific to echo for VHD. However, appropriate assessment of these helps to inform decision-making for timing of intervention. A careful and accurate assessment of these is vital.

The use of Doppler echo techniques is required to confirm the presence of regurgitation, even in an abnormal looking valve on two-dimensional echo. Colour flow imaging is used to demonstrate the regurgitant jet in the relevant cardiac chamber; in the case of MR, it visualises the regurgitation in the left atrium. This should be assessed in at least two anatomical planes, and the echo probe should be manipulated to ensure that any jet is optimally visualised. Using colour Doppler, the direction of the regurgitant jet into the left atrium can be established. An anteriorly directed jet is indicative of posterior leaflet abnormality and vice versa. Colour Doppler can be used to assess severity of MR by regurgitant jet area, measurement of the vena contracta, or by proximal flow convergence.

The size of the regurgitant jet in comparison to the size of the LA has been validated in studies of patients with regurgitation(175, 176). This method has been demonstrated to have a variety of pitfalls, which limit its utility(177). The severity of regurgitation may be underestimated in the presence of jet entrainment along the atrial wall as the jet will appear smaller(176). The type of echo machine in use, and the specific settings on any individual machine (e.g. gain, output power, Nyquist limit) will also affect the appearance of the jet. Jet area is also related to blood

pressure, which is responsible for driving the pressure gradient across the valve. Recording the blood pressure during the echo allows for this to be taken into consideration when interpreting the images. Jet area therefore allows for a semi-quantitive assessment of MR severity, but the limitations of the method should be understood.

Vena contracta (VC) refers to the narrowest diameter of the regurgitant jet, seen at the valve orifice or immediately downstream of it. It reflects the size of the regurgitant orifice, and has been shown to provide an accurate assessment of MR severity(173, 178). VC has been demonstrated to be independent of flow rate and pressure across the orifice(179). It is also less affected by machine settings. Dynamic changes in the regurgitant orifice area may affect the VC(180), an important consideration in mitral valve prolapse with late systolic MR. VC is still accurate for the assessment of acute MR, when jet area is less helpful, and in the assessment of eccentric MR jets. The small size of the VC means that inaccurate measurement may lead to a large error in severity assessment. In order to optimise the assessment and measurement of VC, the use of a narrow sector width of minimum depth, with a zoomed image(33).

The use of the Proximal Isovelocity Surface Area (PISA) method for MR assessment is in common practice, and has been validated in a variety of studies(181-183). PISA relies on the use of colour flow mapping to assess the velocity of blood flow in the left ventricle, as it converges on the regurgitant orifice of the mitral valve. Flow accelerates towards the orifice, and results in a series of “isovelocity” surfaces, which are theoretically hemispheric. More severe regurgitation results in flow acceleration at a greater distance from the valve, and larger PISA shells. Appropriate image quality, and adjustment of the Nyquist limit to optimise visualisation of the PISA, are required, but measurement of PISA can be used to calculate regurgitant volume and effective regurgitant orifice area.

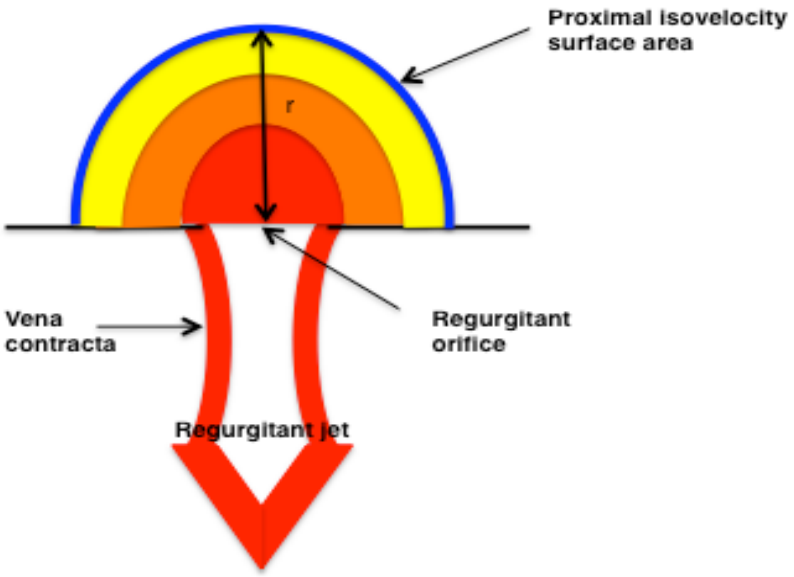

Figure 1.3 Proximal isovelocity surface area (PISA) assessment, demonstrating flow convergence towards the regurgitant orifice, regurgitant jet, and vena contracta; r is the PISA radius.

Like other echocardiographic methods for assessing MR severity, it makes certain geographical assumptions. When the regurgitant orifice changes size and/or shape significantly throughout systole, such as with mitral valve prolapse and late systolic MR, the tendency is for the severity of MR to be overestimated. Non-hemispheric PISA may result from the MR jet being constrained by the ventricular wall on mitral valve leaflet, again leading to an overestimation in the severity of MR. Multiple jets are also challenging for PISA assessment. Each jet requires individual assessment, which is time-consuming, and provides the potential for increased error; in addition overlapping jets will cause further inaccuracies. Mitral valve prolapse with associated MR is an important source of potential error in the use of PISA. Enriquez-Sarano et al demonstrated that regurgitant orifice area by PISA tended to be overestimated in this context, when compared with quantitative Doppler and 2D TTE methods(184). Topilsky looked at outcomes according to the timing of MR in the cardiac cycle, and the associated quantitative echo measures(185). For identical regurgitant orifice area, MR arising in mid-late systole was associated with lower calculated regurgitant volume when compared with MR throughout systole. This was also associated with more benign outcomes. Topilsky et al suggest that in patients

with mid-late systolic MR regurgitant volume may be a more appropriate measure of severity than regurgitant orifice area.

In addition to colour Doppler techniques, the use of pulsed and continuous wave Doppler in the assessment of MR is well recognised. Continuous wave (CW) Doppler can provide indirect evidence of severity through the signal intensity, shapeof the curve, and forward flow velocity across the mitral valve. A poorly defined CW Doppler trace without a complete envelope is seen in the mildest forms of MR, and severe MR is associated with a dense signal which has a similar density to that of the forward flow signal. When looking at the forward velocity across the mitral valve, it is important to look for associated MS, which will increase the velocity. As severity of MR increases, increasing regurgitant volume leads to greater forward flow across the mitral valve. This is associated with an increased forward velocity across the valve, which therefore provides supporting evidence of more severe MR.

The assessment of ventricular filling by pulsed wave (PW) Doppler has also been evaluated in MR. In a study by Thomas et al, the pattern of ventricular filling correlated well with severe MR(186). The finding of a peak E wave velocity of >1.2m/s detected severe MR with a sensitivity and specificity of 86% and 86%, and a positive predictive value of 75%. This study also demonstrated that severe MR was excluded by a filling pattern which had a dominant A wave.

PW can also be useful for the assessment of regurgitant volume and effective regurgitant orifice area (EROA). When PISA is less accurate in cases of eccentric regurgitant jets, or non-hemispherical isovelocity surfaces, the use of PW remains reliable. The difference between transmitral flow, measured at the level of the mitral annulus, and transaortic flow, measured in the LVOT, calculates the regurgitant volume. In order to derive the EROA, the regurgitant volume (by PW) is divided by the velocity time integral of the MR jet (by CW).

Although the quantitation of MR severity by echo is relatively time consuming and prone to errors and inaccuracies, its relevance to outcomes has been well

documented(12, 187-191). However, practitioners need to be aware of the potential pitfalls of methods of quantitation. The reliance on a single indicator of severity should be avoided, and guidelines suggest an integrated approach to their use(33).

1.7.2 Cardiac magnetic resonance

Over recent years, cardiac magnetic resonance (CMR) imaging has become more accessible. It remains relatively costly and time-consuming, when compared to 2DTTE, but it may provide significant additional information, particularly in situations of diagnostic uncertainty. CMR has the ability to provide highly accurate and reproducible measures of left ventricular volumes, mass and systolic function, and provides unparalleled information about the right ventricle(192-195). Like echocardiography, the valve and ventricle can be assessed in the same scan, and the reproducibility of measurements facilitates the follow-up of patients with VHD. It is not limited by acoustic windows or difficulties with alignment of the Doppler beam, although ferro-magnetic implants and significant claustrophobia are contra-indications to CMR. Cawley et al have also demonstrated a lower inter-and intra-observer variability for the assessment of valvular regurgitation compared with TTE(196).

One method for CMR quantitation of MR is by calculating the stroke volume difference, if there is no other valvular regurgitation. Left and right ventricular stroke volumes (LVSV and RVSV respectively) can be calculated from careful contouring of short-axis CMR images. RVSV can be subtracted from LVSV to give the regurgitant volume(RVol):

$$\text{RVol (ml/beat)} = \text{LVSV} - \text{RVSV}$$

Regurgitant fraction (RFrac) can then be calculated as a percentage of LVSV, according to the formula:

$$\text{RFrac (\%)} = (\text{RVol}/\text{LVSV}) \times 100$$

A second method for CMR quantification of MR is the use of phase contrast velocity mapping. Phase contrast velocity mapping allows the velocity of blood moving through the imaging plane to be measured. This is possible as the moving protons

present in the blood flow have a net phase according to the direction of blood flow. The net phase is proportional to the velocity of blood, and is displayed by using different signal intensities to represent different velocities. When flow is moving in the phase-encoding direction set for the image, voxels are bright; flow moving in the opposite direction appears dark. Two sets of images are produced by velocity mapping. Magnitude images permit the borders of the vessel of interest to be visualised. Phase velocity maps display the velocities for each voxel. Images are produced throughout the cardiac cycle. Flow can through the imaging plane can therefore be quantified by identifying a region of interest using the magnitude image. This region of interest is automatically transferred to the phase image. Regions of interest can usually also be automatically transferred to all of the frames acquired, although manual adjustment to individual frames may be required to maximise accuracy. Software for flow quantification integrates the velocities contained within each voxel in the region of interest, and all of the velocities from each frame are then integrated to calculate the total flow through the cardiac cycle. This can be displayed as a flow graph, as well as a display providing peak velocity, forward flow volume and reverse flow volume.

Important limitations of phase contrast velocity mapping include temporal resolution, measuring flow in arrhythmias, and errors of phase shift. The temporal resolution of velocity mapping is approximately one-tenth of Doppler echo, at 25-45ms.This may not be short enough to accurately capture the short time at peak velocity of some stenotic jets. Although measurement of flow in phantoms has been shown to accurately measure flow in excess of 5m/s(197). As flow data are collected across several cardiac cycles, irregular cardiac rhythms can introduce error. In well-controlled arrhythmias, for example well-controlled atrial fibrillation, these errors may not be clinically significant. When arrhythmias have greater beat-to-beat variability, such as with frequent ventricular ectopics, large variations in blood flow can occur, and flow data must be interpreted with caution.

As an alternative to the use of stroke volume difference, phase-contrast velocity mapping may be used to assess valvular regurgitation, and has been shown to be accurate and reproducible for this(198-201). In the case of mitral regurgitation, aortic

forward flow is measured, and this is then subtracted from LVSV to calculate RVol, and subsequently RFrac. In a study comparing stroke volume difference with flow measurement by CMR, Kon et al found the latter to be slightly superior(202). Further discussion of the acquisition of phase contrast velocity mapping in the study presented here is provided in Chapter 5.

1.7.3 Prognostication in mitral regurgitation

CMR quantitation in VHD offers the potential for prognostication, as has been shown by recent work from Myerson et al(203). The ability to predict likelihood of progression to surgery or symptoms by this method may be a very powerful tool, particularly when early intervention with valve repair is feasible. The data presented in Chapter 4 of this thesis demonstrate the potential for CMR quantitation of MR to offer this potential, using data from four high-volume CMR centres in the United Kingdom and New Zealand. Values for RVol and RFrac are presented which discriminate well between those likely to develop indications for surgical intervention, and those who are less likely to do so. Not only do these data demonstrate the potential for identifying those at highest risk of requiring surgery, but may also help to identify those who can potentially be reassured of their low risk of progression.

1.7.4 Comparing methods

Although the pitfalls of TTE assessment of MR are recognised, there are few data comparing them with CMR in this setting. Cawley et al have reported on one such study, which look at both aortic and mitral regurgitation (196), with small number so each, and suggest that CMR may be superior for serial measurements of regurgitation. Van De Heyning et al demonstrated good correlation of planimetry of regurgitant orifice by CMR compared with PISA on TTE, but found TTE to underestimate severity of left ventricular remodelling in these patients(204).

In this thesis, data are presented on a sample of 36 patients with mitral regurgitation, who underwent 2DTTE and CMR assessment of the severity of the MR. The RVol

according to the PISA method on 2DTTE is compared with the RVol measured by CMR. The correlation between these two measures in these 36 patients was not as good as that seen in other studies.

1.8 Aims of this research

This research aimed to investigate the contemporary epidemiology of valvular heart disease in a developed country, and to use advanced cardiac imaging to investigate the assessment of one form of valve disease, namely mitral regurgitation. The main aims were:

- To investigate the prevalence and correlates of valvular heart disease in the population aged 65 years and above, in the Oxfordshire population.
- To examine the extent and predictors of anxiety provoked by screening for valve disease in this population, and to assess the acceptability of trans-thoracic echocardiography in this setting.
- To establish whether quantitation of mitral regurgitation by cardiac magnetic resonance was predictive of progression to surgery or symptoms, and assess the comparability of echocardiographic and CMR measures of regurgitant volume in mitral regurgitation.

1.8.1 Hypotheses

This work was undertaken to test the following hypotheses:

- An increasing prevalence of VHD would be associated with increasing age
- Screening for VHD in patients aged ≥65 years would not be associated with significant anxiety.
- Echocardiography to screen for VHD in the study population would be an acceptable tool.
- Quantitative assessment of mitral regurgitation by cardiac magnetic resonance will be predictive of progression to symptoms or surgery.
- Cardiac magnetic resonance quantitation of mitral regurgitation is comparable to echocardiographic quantitation using the PISA method.

Chapter 2: The OxVALVE Valvular Heart Disease Population Cohort Study: Development and Methods

2.1 Overview

The OxVALVE Valvular Heart Disease Population Cohort Study (OxVALVE PCS) was established as a prospective cohort study to examine the prevalence, incidence and outcomes of participants aged 65 years and above with newly diagnosed valvular heart disease (VHD) in the Oxfordshire population. In addition, developing a well-characterised and annotated database of a large number of cases of VHD, including the full variety of types and severity, is intended to allow the identification of suitable populations for future research studies, including pharmacological, surgical and percutaneous interventions, the use of novel imaging techniques and devices, and even genetic associations. Recruitment began in 2009 and is expected to continue until 2015. The data presented in this thesis are from the first 2500 participants recruited to the study, and focus on the initial findings of the cross-sectional study. As I dedicated a significant amount of time to the setup of the study during my period of research, this chapter describes my involvement in the study development, followed by a description of the study methods.

2.2 Study setup and design

OxVALVE PCS was established as a collaboration between Oxford National Institute of Health Research (NIHR) Biomedical Research Centre (BRC), within Oxford University Hospitals NHS Trust, and the NIHR School for Primary Care Research, within the University of Oxford. Funding support was provided by NIHR BRC, and the NIHR Thames Valley Comprehensive Local Research Network (TVCLRN). As the inaugural research fellow for the study, I was involved in:

- initial study meetings and design

- development of the study protocol
- design of study documentation
- liaison with primary care sites
- procurement of study equipment
- recruitment and initial training and management of members of the study team
- sourcing of data collection and storage solutions
- enrolment and scanning of the initial tranche of study participants

2.3 Initial study meetings and development of study design

2.3.1 Initial study meetings

The concept of OxVALVE involved members of each of the stakeholder groups, spanning primary and secondary care, with input from clinical and research personnel. Meetings to consider the design of the study, what resources would be required to establish and roll out the study, and which primary care sites might be used initially, were attended by members of Oxford BRC, NIHR School of Primary Healthcare Research, and primary care clinicians with involvement in the community echocardiography programme in Oxfordshire, as well as myself as the anticipated inaugural research fellow.

2.3.2 Study design and design of the study documentation

The study design and methods of OxVALVE PCS are fully discussed in in section 2.4. The study design was developed by a group of collaborators from the various stakeholder groups, with consideration being given to identification of potential participants, location and logistical support for the main study visit, maximising uptake by participants, obtaining an optimal dataset, use of questionnaires, feasibility of electrocardiography (ECG) and blood sampling in primary care, and equipment used for each part of the study. As the study design evolved, a study protocol was

developed in order to meet the study objectives, within the logistical and funding constraints identified by the collaborators.

Study documentation was carefully formulated, with close liaison with primary care colleagues, as well as cardiologists. The Patient Information Leaflet (PIL) was composed on a background of potential participants receiving it without prior knowledge of the study. The PIL needed to be comprehensive enough to provide all necessary information, without overwhelming the recipient. This required close liaison with, and feedback from, general practitioners (GPs) in order to achieve an optimal balance.

Consent forms were developed to enable participants to give consent at various levels, according to participant choice. A minimum level of consent was required to allow participants to enrol in the study. The possibility of concern about the storage of blood samples, including deoxyribonucleic acid (DNA), and subsequent follow-up of participants with morbidity and mortality statistics, necessitated a second level of consent which was not mandatory in order to participate in the study. Consent forms were therefore carefully formulated to ensure that participants could clearly understand and indicate their levels of participation in the study.

Results letters to GPs were also required, according to whether participants were found to have an unremarkable ("normal") echocardiogram, VHD (including an indication of severity and the need for clinical referral to arrange follow up), or whether another cardiac abnormality had been detected, which might require further assessment and investigation if it was previously unknown. The study team was sensitive to the fact that participants might be attending the study visit without a cardiovascular diagnosis, but might acquire one as a result of their participation. This had the potential to cause significant levels of anxiety, and therefore results needed to be dealt with sensitively, and communicated to the primary care team in a timely manner, facilitating referral and follow up in secondary care when appropriate.

An information leaflet on VHD was formulated and given to participants who received a new diagnosis of VHD at the end of their study visit. This was intended to

provide some information on VHD, including what the implications of a diagnosis of VHD might have for the participant, and what the next steps might include. This information leaflet provided reassurance to this group of participants, and outlined potential sources of further information.

2.3.3 Liaison with primary care sites

Potential participants were to be identified from GPs' patient lists, which needed to be done by staff within the GP surgeries, as study staff could not have access to identifiable data until participants had given their consent to participate. In order to ensure that patients with previously diagnosed VHD were not inadvertently invited to participate, a list of relevant diagnostic codes was formulated to allow GP staff to identify ineligible patients. This required collaboration with identified members of staff within the initial OxVALVE sites, to ensure that potential participants were correctly identified, and any inappropriate patients, as judged by GPs in the practices, were not sent invitations. Documentation for inviting patients to participate was provided by the study to the GP surgery, to be accompanied by a standard covering letter from the surgery.

The main study visit ('Visit 1') took place in the GP surgery with which a participant was registered. This was felt to be essential in order to maximise patient convenience and comfort, with the likely effect of maximising uptake of invitations to participate. This also allowed study staff to liaise with GPs to highlight clinical issues. As the initial study visit was in primary care, patients booked appointments with the GP surgery directly, in an OxVALVE study 'clinic'. I formulated the clinic requirements, taking into consideration the time required to collect the required data without hurrying the participant. The logistical requirements of space, access to computer systems when necessary, and administrative support for copying of consent forms and reports, were also individual to each participating general practice, and liaison with the first GP surgeries to recruit participants was also a part of my role.

2.3.4 Study equipment

As the study was being established *de novo*, it was necessary to define the equipment and resources required for each part of the study. This ranged from administrative and stationery needs, to echocardiography equipment, data storage solutions, and blood sample processing and storage options. Advice was sought from specialists within each of the relevant areas, prior to decisions being made on what equipment, supplies or resources were most appropriate to the needs and limitations of the study.

A fundamental requirement of the study was for appropriate echocardiography equipment. In order to decide on the optimal system, taking in to consideration the logistical requirements for the unit to be portable and compact, as well as the financial constraints, required interaction with industry representatives. In order to confirm that the technical requirements of the systems met the study's needs, I also consulted with the senior echo specialist at the John Radcliffe hospital. The relevant procurement processes were then followed in order to source the items needed.

2.3.5 Development of the study team

In order to deliver a study of the intended scope of OxVALVE PCS, it was necessary to recruit a study team to deliver the different aspects of the study. The initial members of the study team were myself, as a research fellow, and a research nurse. As the research fellow, I was involved in the recruitment of other study staff, including echocardiographers, the study administrator, a clinical support worker, and study manager.

As early team members were recruited to the team, I was involved in ensuring they were appropriately orientated with all relevant aspects of the study, undertook ICH GCP training, and understood all the relevant aspects of their individual roles. In particular, I was involved in introducing echocardiographers to the study sites and the primary care staff involved in delivery of OxVALVE within the GP surgeries, as well as ensuring that they were all trained in the procedures and standard operating procedures (SOPs) relevant to Visit 1.

2.3.6 Data collection

Data entry from paper data collection into electronic databases has the potential for significant transcription errors to occur. In order to try and minimise the potential for this, we decided to develop electronic case report forms (CRF), which would also negate the need for storage of hard copies. Once the required dataset had been confirmed, the CRFs were developed in collaboration with IT support. The need for data to be captured accurately and concisely directly into a laptop, but without disrupting the rapport developed between the member of study staff and the participant, required careful consideration of the format of the CRF. The design of the CRFs ensured that essential study data had to be input in order to progress through the CRF, and for it to be saved. Use was made of drop-down options when possible, to facilitate speed of data entry. For certain responses, the answer given tailored subsequent questions to ensure that only appropriate questions were asked; for example, if a study participant was entered as male, no questions on pregnancy were asked.

The security of identifiable personal data was considered to be of paramount importance. To this end, the CRF was developed in such a way that personal information, including contact details, was stored separately from the study data. Laptops were encrypted in order to ensure the security of data on the CRFs prior to the data being uploaded.

2.3.7 Echocardiographic image and data storage

The intended number of study participants mandated the provision of significant digital storage for echocardiographic images and data. The size of each echo file was relatively large, and there was a need to have data backed up to ensure that information would not be lost. It was important that solutions put in place at an early stage in the study would be future-proof. Discussions on the amount of storage likely to be required, and the optimal ways in which this could be sourced and supported took place, involving myself as well as representatives from information technology and industry. The need for data to be swiftly and safely uploaded, and then easily

accessed in future for review of echo studies, were important factors in developing a suitable data storage solution for the study's needs.

It was vital that echocardiographic data did not get lost between the point of data capture, and being uploaded to the storage system. It was not possible to upload images directly from the study sites, via a digital link. SOPs were therefore developed to ensure that study personnel operating in the GP practices saved data securely so that it could be transferred to the server without any loss of information.

2.3.8 Enrolment and scanning of participants

Although echocardiographers were to be recruited to the study team, enrolment and scanning began before recruitment could be completed. The initial OxVALVE site was ready to recruit participants, and therefore I undertook the enrolment and echocardiography in the first OxVALVE clinics. This allowed the recruitment of study participants to get underway as soon as it was feasible. I also scanned participants in the second OxVALVE site to come online, to maximise the recruitment rate to the study, and trained new echocardiographers in the completion of the study protocol.

Involvement in the early stages of study recruitment provided the opportunity for any problems with aspects of the study visit, the interactions with primary care, and data collection and storage to be addressed at the earliest opportunity.

My involvement in the study extended throughout all aspects of the study, from early stages of design and setup, through the establishment of the wider OxVALVE team, and including on-site recruitment and echocardiography of study participants. The intention was to ensure that the study was set up in such a way at the beginning, that it could enrol a large number of participants and collect significant amounts of data in the future, without requiring large-scale modifications. It has now enrolled over 3200 participants at six sites since recruitment began in August 2009 and the methodology has now been published.

2.4 Methods

2.4.1 Study setting and participants.

The OxVALVE Study was carried out in a number of general practices within Oxfordshire. The main study visit (visit 1) was held in the general practice where the participant was registered. Setting the screening visit in primary care was desirable in order to maximise uptake of the invitation to participate in the study. A study visit occurring in primary care was also felt less likely to cause significant anxiety amongst participants. Clinical data were collated at visit 1, which also allowed verification of some details by referring to primary care records when necessary.

Those participants newly diagnosed with VHD were invited to attend a follow-up visit at Oxford University Hospitals NHS Trust, which is a secondary and tertiary referral network of hospitals serving the Oxfordshire population, as well as surrounding areas. Attendance at the follow-up hospital-based visit allowed more sophisticated echocardiography, including three-dimensional imaging when possible, as well as 12-lead ECG and blood sampling. The work presented in this thesis relates only to the data obtained at visit 1.

A VHD detection rate of 10% was anticipated, based on data from previous studies. These studies however included only valve disease of at least moderate severity. In OxVALVE, the threshold for inclusion in the screen-positive group was set deliberately low, in order to capture all manifestations of VHD.

2.4.2 Participant selection and rationale

Potential study participants were identified from practice lists in the participating general practice, and the entire registered population of each participating general practice was screened; those aged 65 years old or over, who did not have a documented prior diagnosis of VHD, or who were not deemed to meet the exclusion criteria as judged by GPs, are invited to participate. Potential participants were placed in to a random order, and invited by letter, with a single follow-up reminder to

non-responders. Those who declined to participate were asked to complete a brief response form indicating their reasons for not doing so, in order to detect potential sources of study bias. All patient identifiable information was held by the general practices until participants consented to participate in the study; no telephone contact prior to enrolment in the study was permitted by the Research Ethics Committee.

The rationale for selecting these patients for a study of the prevalence of VHD was based on available data suggesting that, in a developed country, those aged 65 years and above have the highest prevalence of VHD(5, 8). This population group is also anticipated to grow in size over the coming decades, and VHD in this age group is therefore likely to present an increasing burden on health services. Adults under the age of 65 years are also more likely to be in employment, and therefore unable or unwilling to attend a study visit, which would adversely affect the uptake of the study, making it more difficult to draw significant conclusions from the study findings.

Approximately 6,250 patients registered with participating GPs will be invited to participate in the study, with recruitment continuing at the time of writing. An uptake rate of 80% was targeted in the initial sample predictions; this was based on uptake rates from community heart failure screening programmes(205). The sample size was chosen in order to yield an anticipated 500 new cases of VHD, assuming a 10% detection rate of VHD. The resultant cases of VHD allowed prevalence of undetected VHD to be estimated, and demonstrated the patterns of valve lesions and their severity.

2.4.3 Participant recruitment, inclusion and exclusion criteria

Registered patients of participating general practices were prospectively recruited from August 2009, in five general practices within Oxfordshire, according to pre-specified inclusion criteria. Data presented herein are from the first 2500 participants recruited, up to January 2013. Each participant gave written informed consent to be involved.

Subjects were eligible for inclusion in the study if they met the following criteria:

- Aged 65 years or older on the date of the first study visit
- Male or female
- Willing and able to give informed consent to participate in the study
- No documented prior diagnosis of VHD

Subjects were excluded from the study if any of the following applied:

- A previous recorded diagnosis of VHD in primary care, identified using relevant diagnostic codes.
- Terminal illness
- Immobility or general frailty, as judged by the GPs
- Inability or unwillingness to provide informed consent to participate in the study.

Potential symptoms of VHD were not included as an exclusion criterion. The symptoms of valve disease are non-specific, and have other causes, both cardiac and non-cardiac. Chest pain and breathlessness may be due to chest pathology, and pre-syncope may be due to arrhythmia rather than valve disease. In order to use them as an exclusion criterion, these potential symptoms would have had to be coded for consistently on general practice systems. This was felt to be unlikely following consultation with the primary care-based collaborators. Therefore it was decided not to include possible symptoms of VHD in the exclusion criteria to ensure that patients were not inconsistently excluded from invitation, and to avoid excluding those with symptoms due to non-VHD causes.

2.5 Clinical assessment

Participants attended a dedicated research clinic at their registered general practice, were they were assessed by an investigating clinician or a sonographer. All study staff were trained in Good Clinical Practice (GCP), according to International Conference on Harmonisation (ICH) standards. Participants completed an eligibility check, and provided informed consent. Consent could be given at various levels,

according to whether participants wished to give blood samples for storage and DNA testing.

As well as recording baseline demographic information, assessment at the study visit included documenting the following:

- Cardiovascular history
- A list of current medications, with specific reference to cardiac medication
- A smoking history, according to whether the participant has never smoked, or is a current or ex-smoker
- Severity of dyspnoea, according to the New York Heart Association (NYHA) classification
- The presence or absence of chest pain, in accordance with the Canadian Cardiac Society (CCS) score

A focussed physical examination was performed, including:

- Pulse rate and regularity,
- Blood pressure, using an automated sphygmomanometer (Omron M6 blood pressure monitor, Kyoto, Japan)
- height (cm) and weight (kg)
- presence or absence of ankle oedema.

Clinical data were collated using OpenClinica open source software V3.0.4.1 (OpenClinica LLC, Waltham, Massachusetts, USA).

Auscultation was not included in the study visit. This was based on two main factors. The first consideration was that the intention was for the study clinics were to be delivered by sonographers, who would be inexperienced at auscultation. It is recognised that the sensitivity of auscultation for the detection of VHD is limited: Roldan et al reported a sensitivity of only 70% even when performed by a cardiologist(29). Amongst primary care practitioners, auscultation has been shown to be even less reliable(30). Echocardiography however has been demonstrated to improve detection of valve disease(6, 206). Therefore the addition of auscultation by

research sonographers inexperienced in its use was felt not to add sufficient benefit to the study visit.

A transthoracic echocardiogram was then performed, as described below, in section 5. Participants who were found to be in an irregular heart rhythm had a 12-lead electrocardiogram performed.

At the end of the study visit, participants completed study questionnaires.

2.6 Echocardiography

2.6.1 Rationale for using echocardiography

Transthoracic echocardiography remains the gold standard investigation for patients with valvular heart disease, and has been used in epidemiological and outcome studies of VHD(8, 12, 65, 207-209).

Limitations of echocardiography include difficulty in obtaining adequate imaging quality in some cases due to poor acoustic windows, which may lead to difficulties in assessment of the left ventricle (LV), and cardiac valves. Misalignment of the Doppler beam may result in underestimation of trans-valvular flow, particularly across the aortic valve(210).

2.6.2 Echocardiography scan protocol

Comprehensive transthoracic echocardiography was performed by sonographers accredited by the British Society of Echocardiography, using a GE Vivid Q machine (GE Healthcare, Waukesha, WI, USA), equipped with a 2.0-5.0 MHz transducer.

A full echo study was performed according to the British Society of Echocardiography (BSE) Guidelines for Transthoracic Minimum Dataset(211). In addition, the following images and measurements were obtained:

- Zoomed images of the aortic valve, aortic root, and proximal ascending aorta, in the parasternal long and short axis views
- Diastolic function assessment, including pulsed wave (PW) Doppler of the mitral valve inflow, pulmonary vein flow, and tissue Doppler imaging (TDI) of the septal and lateral walls
- Continuous wave (CW) Doppler through the aortic, mitral, and tricuspid valves to demonstrate the presence of regurgitation, in the apical two-, three-, four- or five-chamber views according to the valve being interrogated.

In the presence of normal left ventricular systolic function, the left ventricular ejection fraction (EF) was assessed by the Teichholz equation, alongside visual assessment of overall systolic function. The Teichholz method has been shown to be reliable in this context(212), as has visual assessment by experienced personnel(213). When quantified visually, ejection fraction was classified as follows:

- ≥60%: Normal
- 45-59%: Mild impairment
- 35-44%: Moderate impairment
- <35%: Severe impairment

If systolic function was abnormal on visual assessment, a formal assessment of ejection fraction was performed using biplane volumetric assessment, by Simpson's Method of Discs. EF was quantified for the purposes of providing a clinical report to the participant's general practitioner, but was not used as a categorical preserved/reduced variable for the analysis of the cohort data.

2.6.3 Diagnosis of VHD

During echocardiography, anatomical and physiological assessment of valvular function was performed, according to BSE criteria for assessment of valvular

stenosis and regurgitation(35). Any left-sided VHD, with the exception of 'physiological' regurgitation, was considered significant. Right-sided valvular regurgitation was only considered to be significant if it was of at least moderate severity, and any degree of right-sided valvular stenosis was considered significant. Therefore, patients were considered 'screen positive', i.e. to have a new diagnosis of VHD, if they were found to have any of the following:

- Aortic sclerosis
- Aortic or mitral stenosis or regurgitation of mild, or greater, severity
- Pulmonary or tricuspid stenosis of mild, or greater, severity
- Pulmonary or tricuspid regurgitation of at least moderate severity

Aortic sclerosis was deemed to be present if assessment of the aortic valve detected all of the following:

- focal areas of thickening and calcification of the valve cusps
- normal or near-normal cusp mobility
- maximum transvalvular velocity $\leq$ 2.5 m/s

This definition was based on those used in other studies of aortic sclerosis. Focal areas of thickening and/or calcification with preserved leaflet mobility has been the most consistent descriptor of sclerosis used in these studies(48, 214-217). Not all studies of aortic sclerosis have reported velocities across the aortic valve. In those studies which have used a defined cut-off, the velocity has variously been >1.5m/s(218), 2.0m/s(216, 217), or 2.5m/s(48). The cut-off value of 2.5m/s was chosen to dovetail with the velocity of mild aortic stenosis detailed in the guidelines.

Valvular regurgitation was defined as mild, rather than 'physiological' or 'trivial' , if the regurgitant jet was visible in more than one view on colour flow mapping (CFM), and the jet had a clear origin. If valvular anatomy was normal, and the regurgitant jet extended <1cm into the left atrium, regurgitation was considered to be 'physiological' or 'trivial', and therefore did not meet the criteria for inclusion in the 'screen positive' group.

In order to ensure consistency of reporting of echocardiograms, a rolling review of approximately 15% of scans was undertaken. A random sample of scans was re-reported by a pool of BSE accredited study staff, including sonographers and physicians.

2.7 Questionnaires

Questionnaires were completed by participants at the end of their study visit; these included the short form of the Speilberger State-Trait Anxiety Inventory (STAI)(219), as well as questions related to participants' impressions of screening for VHD. The questionnaires and the rationale for their use is discussed in chapter 4.

Chapter 3: OxVALVE PCS Echocardiographic Results

3.1 Introduction

In this chapter, the echocardiographic findings of the OxVALVE Population Cohort Study will be discussed. Although other studies have attempted to describe the prevalence of VHD within different populations, OxVALVE is the first comprehensive, prospective community-based study of left- and right-sided VHD, including milder forms.

3.2 Methods

As described in chapter 2, 2500 participants, aged over 65 years and with no previous diagnosis of VHD, were recruited from participating GP surgeries in Oxfordshire, between August 2009 and January 2013. In summary, participants attended a study visit in their GP surgery, at which detailed demographics, current health status, and symptomatic status were recorded. A focussed clinical examination was performed, before participants underwent a detailed trans-thoracic echocardiogram.

A low threshold was defined for inclusion in the screen positive group, with any left-sided valve disease considered to be VHD (except for "physiological" regurgitation), and any right-sided stenosis was considered significant. Right-sided regurgitation was only counted as VHD if it was moderate or greater in severity. Calcific aortic valve disease included the full spectrum of disease, from aortic sclerosis (based on the EAE/ASE guidelines(34)) to aortic stenosis (if the maximum transvalvular velocity was ≥2.5m/s).

At the time of data analysis, recruitment was still ongoing into the OxVALVE Study, as ethical approval included recruitment of up to 5000 participants. An interim analysis was performed when 2,500 participants had been recruited. This allowed an

assessment of the breadth of recruitment across age and gender, as well as ethnic groups, to guide future recruitment and targeting of study sites. The analysis at 2,500 was not pre-specified at the outset of the study, but was undertaken when future study sites were being considered. The data for those 2,500 participants are presented here.

3.3 Statistical analysis

Participants were stratified by age and gender to explore the prevalence of VHD in the study population, and by the presence or absence of VHD to examine the demographic and clinical characteristics. Descriptive statistics are presented using means and standard deviations (SD) for continuous variables and counts (percentages) for categorical variables. Student's t-test and Chi-squared test or Fisher's exact test were used to explore dependencies between valve disease and quantitative and categorical variables, respectively. Trends across age groups were examined using the Chi-squared test for trend. Logistic regression models were used to assess the association of the presence of valve disease with demographic and clinical characteristics. All results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs), with a 2-tailed p-value <0.05 considered significant.

3.4 Recruitment

Results for recruitment are based on the first general practice to complete recruiting from their eligible population, and are presented in figure 3.1. From the practice patient database, 2281 patients aged 65 years or older were identified, of which 365 were excluded on the basis of their clinical records; 38% of these were excluded due to having previously diagnosed VHD. Invitations were sent to the remaining 1916 eligible patients, which resulted in a response rate of 52%. There was no response to the invitation to participate from 664 patients (35%), with an additional 11% (208 patients) replying to decline the invitation. Reasons giving for declining to participate were most commonly not wishing to travel to secondary care for a follow up visit if screen positive (although this was stated as being an optional aspect of the study), or having other health problems.

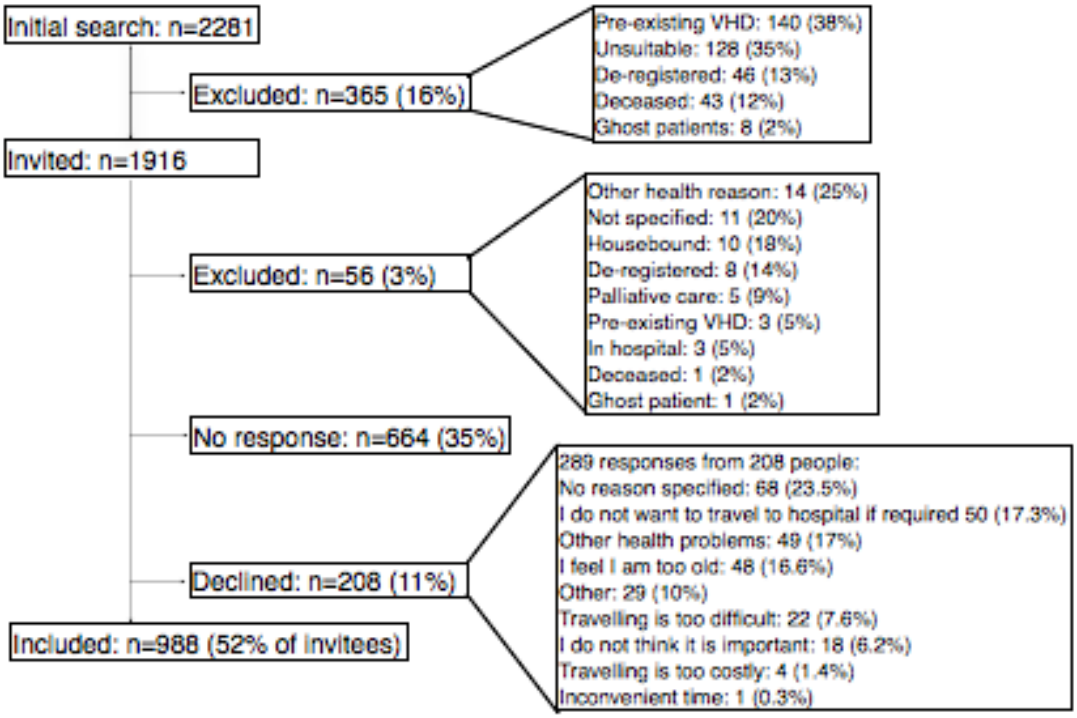

Figure 3.1 Flow chart for first general practice to complete recruitment

3.5 Study population

The demographic data for the first 2500 participants enrolled in the study are presented in Table 3.1 The mean age of participants was 73.0 years (range: 65-95; SD: 6.0), and just over half the participants were female (51.5%); 98.8% of participants classified their ethnic background as White.

Table 3.1 Patient Demographics

Participant Characteristics (N=2500)	N (%)
Gender	
Male	1212 (48.48)
Female	1288 (51.52)
Age Bands, yrs	
65-69	894 (35.76)
70-74	727 (29.08)
75-79	488 (19.52)
80-84	256 (10.24)
85-95	135 (5.4)
Body Mass Index	
BMI <25	778 (31.12)
BMI 25-30	1054 (42.16)
BMI >30	668 (26.72)
Smoking Status	
Non-smoker	1232 (49.28)
Current smoker	174 (6.96)
Ex-smoker	1094 (43.76)

3.6 Health and symptom status

Information regarding health status, including significant past cardiovascular history and drug history, and data on current symptom status was available for all participants, and data are shown in Table 3.2. The most commonly reported cardiovascular conditions were hypertension (44.9%) and hyperlipidaemia (35.7%). Diabetes mellitus was reported by 11.3% of participants, with only 1.8% reporting a known history of rheumatic fever. Only 109 participants (4.4%) reported a history of atrial fibrillation. On questioning about symptom status, only 64 participants (2.6%)

described NYHA class III/IV symptoms, and only 5.16% had a CCS score of 1 or more.

Table 3.2 Health and symptom status

History		
Diabetes mellitus	282	(11.3%)
Hypertension	1123	(44.9%)
Hyperlipidaemia	892	(35.7%)
Atrial fibrillation	109	(4.4%)
Myocardial infarction	131	(5.2%)
Coronary angiography	224	(9.0%)
Percutaneous coronary intervention	97	(3.9%)
Coronary artery bypass grafting	47	(1.9%)
Angina	213	(8.5%)
Stroke/TIA	155	(6.2%)
Rheumatic fever	45	(1.8%)
Pacemaker	14	(0.6%)
NYHA Class		
NYHA I/II	2436	(97.4%)
NYHA III/IV	64	(2.6%)
CCS Score		
0	2371	(94.8%)
I/II	120	(4.8%)
III/IV	9	(0.4%)

All values are expressed as numbers (%) for presence of variable
TIA: Transient ischaemic attack; NYHA: New York Heart Association; CCS: Canadian Cardiovascular Society

3.7 Medication and examination findings

Current drug histories were obtained from all participants, although data regarding blood pressure were unavailable on 5 participants, as a result of the machine being unable to obtain a measurement. Data on medication and examination findings are shown in Table 3.3.

Table 3.3 Medication and examination findings

Medication	
Lipid lowering agent	948 (37.9%)
ACEi	579 (23.2%)
ARB	262 (10.5%)
Anticoagulant	65 (2.6%)
Aspirin	541 (21.6%)
Beta blocker	390 (15.6%)
Calcium channel blocker	380 (15.2%)
Diuretic	451 (18.0%)
Nitrates	133 (5.3%)
Other anti-platelet	35 (1.4%)
Examination findings	
Heart rate (bpm)	72.8 (11.8)
Systolic blood pressure (mmHg)	140 (19.4)
Diastolic blood pressure (mmHg)	79.5 (11.3)
Ankle oedema	305 (12.2%)
Body mass index (kg/m^2)	27.6 (5.0)
Sinus rhythm	2408 (96.3%)
Atrial fibrillation	83 (3.3%)
Paced rhythm	9 (0.4%)

All values are expressed as numbers (%) for presence of the variable, or mean±SD
ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker;

3.8 Echocardiographic findings

All participants underwent transthoracic echocardiography, although difficulty obtaining diagnostic images in a proportion of participants resulted in some data points being unavailable (less than 25/1% for the majority of structures or measurements). Reasons for inability to obtain diagnostic images include: co-existing pulmonary disease, obesity, and a large left-sided pleural effusion. A full BSE dataset(211) was obtained, with 2D, Doppler, colour flow mapping and M-mode measurements included. Assessment of valvular function, and quantification of valve lesions was undertaken according to BSE guidelines for the assessment of VHD(35). Data relating to ejection fraction, septal thickness, left ventricular end diastolic dimension, left atrial dimension, and left ventricular mass and mass index are shown in table 3.4.

Table 3.4 Echocardiographic findings

Ejection fraction (%)	67.2 (8.7)
IVSd (mm)	10.0 (2.3)
LVEDd (mm)	46.0 (7.2)
LA diameter (mm)	37.0 (6.5)
LV mass (g)	154.5 (53.2)
LV mass index (g/m^2)	81.8 (25.3)

Total number of participants analysed for these variables was between 2478 and 2485;
All values are presented as mean±SD;
IVSd: inter-ventricular septal thickness in diastole; LVEDd: left ventricular end diastolic dimension; LA: left atrium; LV mass: left ventricular mass; LV mass index: left ventricular mass indexed to body surface area

3.9 Prevalence of newly diagnosed valvular heart disease

Some form of valvular heart disease was diagnosed in just over half of the participants (50.8%), according to the study criteria described in chapter 2. The majority of newly diagnosed VHD was mild in severity, although in 159 participants (6.4%) new VHD of moderate or greater severity was detected. Aortic sclerosis was the most common new diagnosis, affecting 34% of the cohort. Mitral regurgitation was diagnosed in 22.1% of the cohort (19.8% mild MR, 2.3% moderate or severe MR), and aortic regurgitation was detected in 15.2% of participants (13.6% mild AR, 1.6% moderate or severe AR); 32 participants (1.3%) were found to have previously undiagnosed aortic stenosis, of which 17 (0.7%) had AS that was moderate or severe. Bicuspid aortic valve was detected in 8 participants (0.3%). Mitral stenosis was detected in only 9 participants (0.4%). Right-sided valve disease was uncommon in study participants, with tricuspid regurgitation being the most common (2.7% moderate TR); no tricuspid or pulmonary stenosis was detected. Table 3.5 shows data for the prevalence of newly diagnosed VHD in this cohort.

Table 3.5 Prevalence of newly diagnosed valvular heart disease

Any form of VHD	
None	1231 (49.2)
Mild	1110 (44.4)
Moderate/Severe	159 (6.4)
Aortic Sclerosis	
None	1649 (66.0)
Mild	795 (31.8)

Table 3.5 Prevalence of newly diagnosed valvular heart disease

Moderate	51 (2.0)
Severe	5 (0.2)
Aortic Stenosis	
None	2468 (98.7)
Mild	15 (0.6)
Moderate	13 (0.5)
Severe	4 (0.2)
Aortic Regurgitation	
None	2118 (84.7)
Mild	341 (13.6)
Moderate	40 (1.6)
Severe	1 (0.04)
Bicuspid Aortic Valve	
No	2492 (99.7)
Yes	8 (0.3)
Mitral Stenosis	
None	2491 (99.6)
Mild	7 (0.3)
Moderate-severe	2 (0.1)
Mitral Regurgitation	
None	1948 (77.9)
Mild	494 (19.8)
Moderate	55 (2.2)
Severe	3 (0.1)
Tricuspid Regurgitation	
None	1429 (57.3)
Mild	599 (24.0)
Moderate	67 (2.7)

Table 3.5 Prevalence of newly diagnosed valvular heart disease

Pulmonary Regurgitation		
None	1932	(77.3)
Mild	561	(22.4)
Moderate	7	(0.3)

All values are presented as numbers (%) for the variable

More than one valve lesion was detected in 38.5% of participants. This was most common in aortic regurgitation, in which 81% had at least one other form of VHD. Over half of those with mitral regurgitation (58%), and 47% of those with AoScl also had at least one other valve lesion found.

3.10 Associations with newly diagnosed valvular heart disease

Univariate analysis was performed to look at associations with a new diagnosis of VHD. As expected, increasing age was significantly associated with a new diagnosis of VHD. In the youngest age band 42.4% of participants were screen positive, but over three quarters (76.3%) of those aged 85-95 years were found to be so. Increasing age was also associated with an increased likelihood of moderate or more VHD. This association held true for all forms of VHD detected, with the exception of PR due to the small number of participants with significant PR. These associations are shown in Table 3.6 and Figure 3.2 (data for MS and PR are not included due to the small numbers).

Table 3.6 Association of age with prevalence and severity of VHD

Age bands	65-69	70-74	75-79	80-84	85-95	
n	894	727	488	256	135	
Any VHD, %	42.4	45.8	57.4	68.0	76.3	p<0.001
Moderate/Severe VHD, %	2.5	4.4	7.8	13.7	23.7	p<0.001
Moderate/Severe MR, %	1.0	1.7	3.3	4.7	6.7	p<0.001
Moderate/Severe AS, %	0.3	0.7	0.0	1.6	3.7	p<0.001
Moderate/Severe AR, %	0.7	1.0	1.6	4.7	5.9	p<0.001

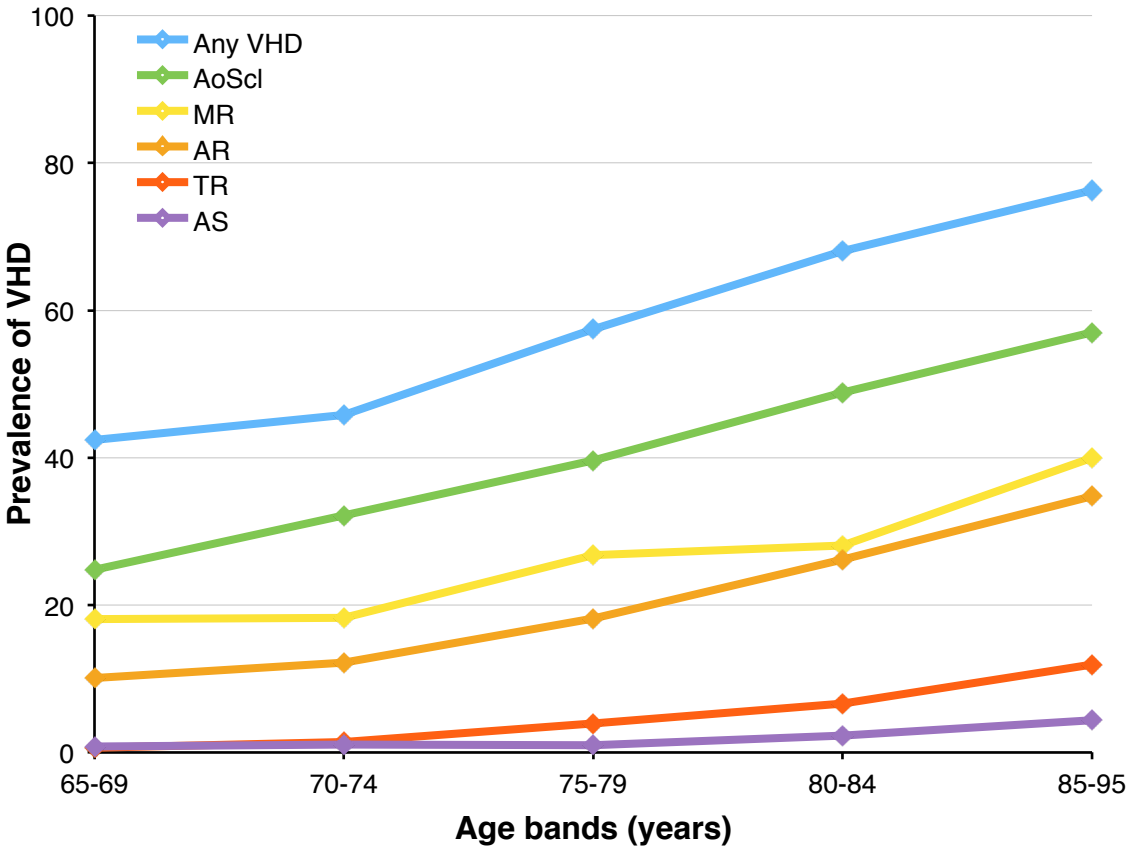

Figure 3.2 Prevalence of any VHD, MR, AS, AoScl, AR and TR by age

Data relating to associations of new diagnosis of VHD with other demographics and health status are presented in table 3.7. On univariate analysis, a significantly greater likelihood of a new diagnosis of VHD was associated with a history of hypertension, hyperlipidaemia, AF, MI, coronary angiography, CABG, and stroke/TIA. There was no association with gender, diabetes mellitus, percutaneous coronary intervention or angina.

Table 3.7 Association of demographics and health status with newly diagnosed VHD

	No VHD		VHD		p-value
Gender					
Males	612	(50.5%)	600	(49.5%)	
Females	619	(48.1%)	669	(51.9%)	0.239
Smoking status					
Non-smoker	586	(47.6%)	646	(52.4%)	
Current smoker	101	(58.0%)	73	(42.0%)	
Ex-smoker	544	(49.7%)	550	(50.3%)	**0.032**
HIstory					
Diabetes mellitus	143	(50.7%)	139	(49.3%)	0.645
Hypertension	508	(45.2%)	615	(54.8%)	**<0.001**
Hyperlipidaemia	413	(46.3%)	479	(53.7%)	**0.032**
Atrial fibrillation	35	(32.1%)	74	(67.9%)	**<0.001**
Myocardial Infarction	51	(38.9%)	80	(61.1%)	**0.02**
Coronary angiography	86	(38.4%)	138	(61.6%)	**<0.001**
Percutaneous coronary intervention	42	(43.3%)	55	(56.7%)	0.276
CABG	15	(31.9%)	32	(68.1%)	**0.024**
Angina	101	(47.4%)	112	(52.6%)	0.628
Stroke/TIA	60	(38.7%)	95	(61.3%)	**0.009**
Rheumatic fever	20	(44.4%)	25	(55.6%)	0.618

Table 3.7 Association of demographics and health status with newly diagnosed VHD

NYHA Class			
I/II	1196 (49.1%)	1240 (50.9%)	
III/IV	64 (54.7%)	29 (45.3%)	0.449

All values are expressed as numbers (%); p-value <0.05 was considered significant
TIA: Transient ischaemic attack; NYHA: New York Heart Association; CABG: Coronary Artery Bypass Graft

A multiple regression analysis was performed to look at factors associated with any valvular heart disease, the results of which are shown in Table 3.8. Increasing age, female gender, previous angiography, systolic blood pressure and atrial fibrillation were all associated with an increased likelihood of VHD, as were increased septal thickness, increasing left ventricular mass and mass index, and increased left ventricular diameter. A history of angina, and a higher heart rate, higher diastolic blood pressure and presence of ankle oedema on clinical examination were associated with a reduced likelihood of a new diagnosis of VHD.

Table 3.8 Regression analysis for a new diagnosis of VHD

	OR	95% CI	p-value
Age, yrs	1.39	(1.29,1.50)	<0.001
Female gender	1.60	(1.33,1.92)	<0.001
History			
Angina	0.58	(0.40,0.83)	0.003
Coronary angiography	1.69	(1.18,2.41)	0.004
Examination findings			
Heart rate, bpm	0.85	(0.79,0.92)	<0.001
Systolic blood pressure, mmHg	1.11	(1.05,1.18)	<0.001
Diastolic blood pressure, mmHg	0.88	(0.80,0.97)	0.010

Table 3.8 Regression analysis for a new diagnosis of VHD

Ankle oedema	0.66	(0.51,0.86)	0.002
Atrial fibrillation	2.59	(1.52,4.42)	<0.001
Echocardiographic findings			
IVSd, mm	1.10	(1.06,1.14)	<0.001
LVEDd, mm	1.03	(1.02,1.05)	<0.001
LV mass, g	16.3*	(12.4,20.2)	<0.001
LV mass index, g/m^2	9.5*	(7.6,11.5)	<0.001

Results are presented as odds ratios (OR), with the corresponding 95% confidence interval (CI); p-value <0.05 was considered significant
OR for age is per 5 yrs increase; OR for heart rate is per 10bpm increase; OR for blood pressure is per 10mmHg increase; OR for IVSd and LVEDd is per mm increase
IVSd: Inter-ventricular septum, diastole; LVIDd: left ventricular end diastolic dimension; LV mass: left ventricular mass; LV mass index: left ventricular mass indexed to body surface area; * Denotes Effect size rather than OR, due to continuous nature of the variable

3.11 Associations with individual left-sided valve lesions

Multiple regression analysis was performed for each valve lesion. Due to the small numbers of right-sided VHD and mitral stenosis, data are only presented for aortic valve lesions and mitral regurgitation. All individual lesions were associated with increasing age, as shown below in the tables relating to individual lesions.

3.11.1 Associations with mitral regurgitation

Mitral regurgitation was associated with an increased likelihood of female gender (OR: 1.68; 95%CI: 1.24-2.27; p=0.001). It was also strongly associated with an increased likelihood of atrial fibrillation (OR:3.49; 95% CI: 2.03-5.97; p<0.001). Analysis of echocardiographic findings demonstrated an association between increasing left atrial size, increasing septal thickness, increasing left ventricular size, and increasing left ventricular mass and mass index. MR was also associated with

increasing LV mass and mass index when stratified by severity, looking at mild MR or moderate & severe MR. Unexpectedly, current smoking status was associated with a lower likelihood of mitral regurgitation, as was increasing body mass index. A lower likelihood of MR in those who were ex-smokers did not reach statistical significance.

Table 3.9 Regression analysis for associations with mitral regurgitation

N=2461	OR	95% CI	p-value
Age, yrs	1.03	(1.01,1.05)	0.001
Female gender	1.68	(1.24,2.27)	0.001
Smoking status			
Current smoker	0.58	(0.36,0.92)	0.021
Ex-smoker	0.80	(0.65,1.00)	0.052
Examination findings			
Atrial fibrillation	3.49	(2.03,5.97)	<0.001
BMI, kg/m^2	0.90	(0.87,0.92)	<0.001
Echocardiographic findings			
LA size, cm	1.36	(1.13,1.64)	0.001
IVSd, cm	2.05	(1.25,3.34)	0.004
LVEDd, cm	1.70	(1.44,2.00)	<0.001
LV mass, g (mild MR)	13.7*	(8.8,18.6)	<0.001
LV mass, g (moderate/severe MR)	15.8*	(2.8,28.8)	0.02
LV mass index, g/m^2 (mild MR)	9.5*	(7.13,12.0)	<0.001
LV mass index, g/m^2 (moderate/severe MR)	13.5*	(7.1,19.9)	<0.001

Results are presented as odds ratios (OR), with the corresponding 95% confidence interval (CI); p-value <0.05 was considered significant
OR for age is per 5 yrs increase; OR for IVSd and LVEDd is per cm increase IVSd: Inter-ventricular septum, diastole; LVEDd: left ventricular end diastolic dimension; LA: left atrium; BMI: Body Mass Index; LV mass: left ventricular mass; LV mass index: left ventricular mass indexed to body surface area; * Denotes effect size rather than OR, due to continuous nature of the variable

3.11.2 Associations with aortic regurgitation

In aortic regurgitation, multiple regression analysis demonstrated an increase in likelihood of AR with increasing LV size. There was also a significant association between a new diagnosis of AR and increasing LV mass and mass index. This association was more pronounced when the LV mass was examined in the presence of moderate or severe AR. A new diagnosis of AR was less likely in those who were ex-smokers, but this did not reach statistical significance in those who were current smokers. Gender was not significant for the likelihood of a new diagnosis of AR.

Table 3.10 Regression analysis for associations with aortic regurgitation

N=2477	OR	95% CI	p-value
Age, yrs	1.09	(1.07,1.11)	<0.001
Smoking status			
Current smoker	0.77	(0.47,1.26)	0.295
Ex-smoker	0.76	(0.60,0.96)	0.023
Echocardiographic findings			
LVEDd, cm	1.17	(1.02,1.35)	0.028
LV mass, g (mild AR)	7.4*	(1.7,13.1)	0.01
LV mass, g (moderate/severe AR)	43.4*	(28.2,58.5)	<0.001
LV mass index, g/m^2 (mild AR)	5.2*	(2.4,8.1)	<0.001
LV mass index, g/m^2 (moderate/severe AR)	26.3*	(18.8,33.7)	<0.001

Results are presented as odds ratios (OR), with the corresponding 95% confidence interval (CI); p-value <0.05 was considered significant
OR for age is per 5 yrs increase; OR for LVEDd is per cm increase LVEDd: left ventricular end diastolic dimension; LV mass: left ventricular mass; LV mass index: left ventricular mass indexed to body surface area; * Denotes Effect size rather than OR, due to continuous nature of the variable

3.11.3 Associations with aortic stenosis

Aortic stenosis was only significantly associated with increasing age, a current smoking history, and increased left atrial size, when non-significant terms were excluded. There was a trend towards a decreased likelihood of aortic stenosis in ex-smokers, but this did not reach statistical significance. Regression analysis to look for an association between a new diagnosis of AS and LV mass also did not reach statistical significance; this is likely to be due to the low numbers of participants with AS, particularly moderate or severe AS. Increased LA size is linked to AS due to increased left-sided filling pressures.

Table 3.11 Regression analysis for associations with aortic stenosis

N=2485	OR	95% CI	p-value
Age, yrs	1.09	(1.03,1.15)	0.001
Smoking status			
Current smoker	3.12	(1.1,8.85)	0.032
Ex-smoker	0.48	(0.21,1.08)	0.077
Echocardiographic findings			
LA size, cm	2.27	(1.60,3.23)	<0.001

Results are presented as odds ratios (OR), with the corresponding 95% confidence interval (CI); p-value <0.05 was considered significant
OR for age is per 5 yrs increase; OR for LA size is per cm increase; LA: Left atrium

3.12 Discussion

The findings of this study demonstrate that:

1) Valvular heart disease is highly prevalent in those over the age of 65 years, although the majority of this is mild.
2) Increasing age is associated with an increasing prevalence of VHD.
3) Valvular regurgitation is the most commonly detected form of VHD in the community-based population.

4) Female gender, lower BMI, and atrial fibrillation are associated with significant increased likelihood of mitral regurgitation.
5) Aortic stenosis, but not other forms of left-sided VHD, is associated with a current smoking status.
6) Mitral and aortic regurgitation are associated with increasing left ventricular mass.

3.12.1 High prevalence of VHD

This study is the first prospective, community-based study of valvular heart disease investigating the prevalence of left- and right-sided VHD, and including the whole spectrum of disease. Although previous studies have attempted to ascertain similar data, they have been retrospective(8, 9, 16), hospital based(5), focussed on the investigation of non-valvular heart disease(18), or only aimed at aortic valve disease(9, 16, 20, 41).

Over half of participants (50.8%) in this study were found to have previously undetected VHD, which is higher than in other studies. Nkomo et al(8) report a prevalence of 13.2% in those aged over 75, which is much lower than the 63.4% detected in the same age group by OxVALVE. However, Nkomo et al excluded milder forms of VHD. Within the OxVALVE study, moderate or greater VHD was detected in 11.9% of those of the same age, which is comparable to those noted by Nkomo, when taking into consideration that OxVALVE excluded those with a previous known diagnosis of VHD. However other studies, particularly those looking at aortic stenosis, have suggested higher prevalences than this. In a 2013 meta-analysis looking at aortic stenosis prevalence from the point of view of demand for trans-catheter aortic valve implantation, Osnabrugge et al found a prevalence of 12.4% in those aged ≥75 years, of which 3.4% was characterised as severe(220); the Reykjavik-AGES study found similarly high prevalences(20). Differences in prevalence between different cohorts are likely to represent different populations being studied, and different methods of assessment and grading of severity for aortic stenosis. The population studied by OxVALVE were asymptomatic and community-based, and those with previously detected disease, either due to a murmur being

heard or symptoms being investigated, were excluded. Those who were more frail or unwell may have chosen not to participate in the study, leading to potential selection bias and lower prevalence of significant VHD of all types.

The finding of moderate or severe VHD in 6.4% of the study population suggests that there is a significant burden of undetected clinically relevant VHD in this age range. Even in the youngest age group, 2.5% were found to have VHD which was graded as moderate or severe. Over the remainder of their life expectancy, this may reach criteria for intervention, and should be followed up with this in mind. Increasing numbers of interventions for VHD are being carried out even in the oldest age groups, with improving outcomes(37), confirming the importance of timely detection of VHD in this population.

Although the majority of VHD detected in this study was mild, when subjects with known VHD from the community were included the prevalence of clinically significant VHD increased to 11.3%. The protracted and unpredictable nature of VHD requires serial testing in order to monitor disease progression and ensure timely intervention if required. Monitoring in such large numbers of patients will require investment in echocardiographic services and valve clinics, and the costs of this will be considerable. However, the costs of appropriate surveillance and intervention may be offset by savings in the cost of hospitalisations and treatment for heart failure for VHD, as discussed in section 3.12.7. There is also evidence to suggest that over-investigation of VHD may occur, alongside practices which do not adhere to guidelines on the management of VHD(221). This suggests that significant cost savings could be made in valve surveillance, as has been demonstrated by Taggu et al(222), when services are optimally managed.

In a publicly funded healthcare system with finite resources, consideration needs to be given to which patients are most appropriate to follow up with routine surveillance. Some patients in the oldest age groups may feel that they would not wish to have any treatment for VHD if they reached criteria for surgical or percutaneous intervention. In these cases where symptoms would be treated medically, sensitive discussions between clinical and patient may lead to a decision

not to follow up the VHD on a routine basis. These discussions should take place between patients and specialists in order to ensure that patients are apprised of all of the factors which might influence their decision. Conversely, those who are reluctant to consider possible intervention, but who are otherwise suitable candidates for repair of replacement of their valve, require a suitable appreciation of the ramifications of not having treatment.

To provide access to a streamlined service providing appropriate patient evaluation and serial testing, ensuring the timely consideration of intervention with prompt referral to a surgeon as appropriate, and provide patients with vital education both pre- and post-surgery may be best achieved through a specialist valve clinic delivered by a multidisciplinary team. This is in keeping with similar models used for heart failure, arrhythmias and coronary disease, and is recommended by national and international societies(223, 224). Establishing clinics such as these will allow the concentration of expertise in VHD, ensuring that training and education are optimised and practices are kept up to date. This does not mean that such service delivery should be restricted to tertiary centres. A 'hub and spoke' model with satellite clinics for surveillance having strong links with a specialist centre will ensure maximal accessibility to optimal expertise. Accessibility in the older age groups is likely to be of particular importance. In individuals who may have other comorbidities to take into account when considering intervention, access to those with the greatest experience in managing such cases is also of greatest value.

The potential costs of follow up of large numbers of patients with VHD highlights the need for further work on risk factors and markers for more rapid progression, or decompensation. The ability to identify those most at risk of rapid progression and who will meet indications for intervention for VHD will help to avoid high costs associated with management of LV dysfunction, prolonged hospital stays and difficult post-operative course. Conversely, the identification of those who are less likely to progress to severe disease, symptom development or reaching surgical criteria will also facilitate the rationalisation of resource allocation. Less frequent follow up in those with a more benign phenotype would result in better use of

investigations and out-patient time, as well as freeing the patients from an unnecessary frequency of follow up.

3.12.2 Increasing prevalence with increasing age.

The strong association of age with prevalence of VHD is in line with those demonstrated in previous retrospective studies of VHD(5, 8, 9, 18, 20, 41, 225). This association was demonstrable for all valve lesions. Increasing age was also associated with an increased likelihood of VHD of greater severity. This is in keeping with degenerative disease as the major aetiology of VHD in developed countries, as previously demonstrated in the hospital-based Euro Heart Survey(5). The AGES-Reykjavik study demonstrated a rapid increase in prevalence of severe AS with age, with a prevalence of 0.92% in those aged under 70 years, to 7.3% in those ≥80 years of age(20). Using population projections, they suggest that the numbers of patients affected by severe AS will triple by 2060. Such a potentially large number of patients requiring management of their AS is likely to put a great burden on any healthcare system, financially and logistically, and demands in-depth planning to avoid being overwhelmed.

When compared with the wider population, both within Oxfordshire and across England and Wales, the study population was younger, with a larger proportion of study participants being under the age of 75 than in the general population. Those invited to participate in the study who declined to participate were invited to provide feedback on reasons for declining. A frequently sited reason for declining to participate was being too old, or having other co-morbidities. This was anticipated when designing the study information for patients. It was specifically stated that participants of all ages would be valuable to the study, and it was also specified that the cost of any transport to study appointments could be claimed, including taxis. Despite this, some invitees stated that their age and difficulty with travelling to the general practice were barriers to participation.

Increasing age is associated with increased co-morbidities, and this also contributed to an overall younger population responding to the study invitation. Census data are

gathered without respondents needing to leave their own home, but participation in the OxVALVE study required travel and mobility. Some decliners felt that they had too many other health problems to feel able to participate in the study, and this is likely to have resulted in the proportion of older age groups being smaller than in the general population. Prior to study invitation letters being sent out to invitees, primary care practitioners also reviewed the list of eligible patients on the practice list. If they were aware of any of their patients with significant frailty or co-morbidities, those patients were excluded from the invitation process. This is also reflected in the ages of those who eventually chose to participate in the study.

Table 3.12 Comparison of age of OxVALVE participants with Oxfordshire population and population of England and Wales

Age Bands, yrs	**OxVALVE participants**	**Oxfordshire population**	**Population of England and Wales**
65-69	35.8	29.1	29.0
70-74	29.1	23.4	23.6
75-79	19.5	19.0	19.3
80-84	10.2	14.4	14.5
≥85	5.4	14.2	13.6

Results are expressed as percentages. N=2500 for OxVALVE participants.
Data for Oxfordshire population, and population of England and Wales taken from Office of National Statistics National Census 2011 data.

If such a high prevalence of VHD is seen within this population, does it in fact represent part of the spectrum of 'normal'? The term 'degenerative' has previously been widely used to describe some forms of VHD, in particular AS. Recent advances in understanding of the underlying processes of VHD have led to this being used less commonly. The inflammation demonstrated in AS, leading on to fibrosis and calcification, and even subsequent bone formation in very advanced disease, suggest that this is a truly pathological process, and far from normal. Such changes are found in AS in all age groups, and so cannot be considered a part of the ageing process.

The mechanisms underlying aortic and mitral regurgitation are less well elucidated, and structural abnormalities are more heterogeneous. Leaflet prolapse, myxomatous degeneration of the valve, chordal rupture, or even no clear identifiable cause even on pathological examination: any of these may give rise to valvular regurgitation. Again, these processes are seen in all age groups. They should not simply be attributed to age, or one end of the spectrum of normality.

3.12.3 High prevalence of valvular regurgitation

In the OxVALVE cohort, the most commonly detected valve lesions were mitral and aortic regurgitation. Although in a hospital-based study, Iung et al found AS to be the commonest form of VHD(5), community-based studies have consistently demonstrated higher prevalences of mitral and aortic regurgitation(8, 18, 225).

As part of the Strong Heart Study, Lebowitz et al found AR in 14.4% of participants aged >60 years old(18), which is comparable with our detected prevalence of 15.3%. Singh et al found a prevalence of approximately 10.8% in those over the age of 60(225), although with a higher prevalence of moderate or greater severity.

Jones reports a prevalence of mitral regurgitation of approximately 28% in those aged ≥65 years old(19), which is higher than the prevalence detected in our study, despite similar echocardiographic criteria. Although ethnic differences might be considered to be responsible, the Framingham Heart Study participants are of a similar ethnic mix to our study population, but reported a prevalence of MR of 27% . in those aged over 60(225). Nkomo reported a prevalence of 7.3% in those aged ≥65 years of age(8), although this study had a higher threshold for detection of disease.

A small but significant proportion of the newly diagnosed regurgitation in our cohort was of moderate or greater severity (2.3% moderate/severe MR; 1.6% moderate/severe AR). This corresponds to the severity of disease found in the Strong Heart Study(18, 19), although Singh suggests a similar prevalence of moderate or greater aortic regurgitation, and mitral regurgitation in women, but a higher prevalence of more severe MR in participants of male gender(225).

3.12.4 Female gender, body mass index and atrial fibrillation are associated with mitral regurgitation.

In this study population, multiple regression analysis showed significant associations between mitral regurgitation and female gender, body mass index and atrial fibrillation.

Female gender has previously been demonstrated to be associated with an increased risk of regurgitant valve disease in only one other epidemiological study of VHD(19). Aortic regurgitation has been linked to male gender in participants in the Framingham Heart Study(225), but this study showed no gender association with mitral regurgitation. Nkomo found that overall VHD was diagnosed less often in women in the community-based setting, and this was evident for mitral and aortic regurgitation(8). In Great Britain and Ireland, only 30% of those undergoing mitral valve repair for degenerative mitral valve disease, and 40% of those undergoing mitral valve replacement, are female(37). The discrepancy between these statistics and our data would suggest that women may be under-treated for mitral valve disease, or may present too late for beneficial intervention.

Atrial fibrillation resulting from significant mitral regurgitation is thought to relate to increased left atrial pressure and stretch. This study also showed a significant relationship between left atrial size and mitral regurgitation. In 2004, Parkash et al showed a correlation between the risk of onset of atrial fibrillation and left atrial size(226), and MR, LA size and onset of AF are clearly inter-related. There is a possibility that AF itself results in a type of "functional" MR, which resolves when sinus rhythm is restored(227), although it is likely that a much greater proportion of MR that co-exists with AF is primary, organic MR. The risk of significant MR developing associated atrial fibrillation is approximately 5% per year(228, 229). The onset of atrial fibrillation in severe asymptomatic MR is an indication for surgery according to current guidelines(230) (Class of recommendation: IIa). There is some evidence that atrial fibrillation at the time of intervention is associated with worse outcomes(231, 232), although this may be offset by concomitant AF intervention at the time of surgery(233).

The data presented here suggest that in patients with newly-diagnosed AF, echocardiography to look for associated valve disease is a worthwhile undertaking. This approach is in keeping with international guidelines for the management of AF(234, 235). However, the current UK guidelines from the National Institute of Health and Care Excellence suggest that routine echocardiography is not necessary(236). As stated in Chapter 2, auscultation is unreliable even in relatively skilled hands(29, 30), and therefore it cannot be relied upon in isolation to detect VHD. Unless echocardiography is routinely performed in those with newly diagnosed AF, it is likely that VHD will continue to be missed in a proportion of these patients.

In this population-based screening study for VHD, multiple regression analysis demonstrated an association between body mass index and mitral regurgitation (OR 0.90, 95% CI 0.87,0.92, $p<0.001$). This suggests that for every unit increase in BMI, there is a 10% decrease in the likelihood of a new diagnosis of mitral regurgitation. This is consistent with the findings of the other studies on mitral regurgitation discussed above(19, 225). The cause for this association remains unclear.

3.12.5 Aortic stenosis and smoking status.

Aortic stenosis was the only valve lesion to have a positive correlation with current smoking status in the OxVALVE Study. In studies looking at associations with regurgitation, there has been no evidence of a positive correlation between either aortic regurgitation(225) or mitral regurgitation(19). However, the link between aortic stenosis and smoking has been demonstrated in several previous studies. Stewart et al demonstrated a 35% increase in the risk of aortic stenosis in smokers(42), and it has also been shown to shown to be associated with calcification of the aortic valve, although not with progression of calcification(97).

Aortic stenosis has been shown to share risk factors with atherosclerotic disease(42), and smoking is a well-established risk factor for atherosclerosis. The pathophysiological mechanisms underlying AS also resemble those seen in atherosclerosis(237). This is results in a high percentage of patients with significant

AS having concomitant coronary artery disease (CAD): over half of those over the age of 70 in a Scandinavian study(11), and over 40% in those aged 80 or over in a British series(238). Despite this close histological and epidemiological relationship, medical interventions - most notably statin therapy - have not provided the same benefit for the treatment of AS as for CAD(79, 239, 240).

3.12.6 Left ventricular mass and VHD.

A diagnosis of aortic or mitral regurgitation was associated with increasing left ventricular mass and mass index. Overall a diagnosis of VHD was associated with a significantly higher LV mass, although no statistically significant difference was found between the LV mass of those with or without AS.

It would be expected to find a positive correlation between a diagnosis of AS and LV mass or mass index. In AS, the decreasing valve area with progressive stenosis results in a gradually increasing pressure gradient across the valve. As discussed in Chapter 1, the LV hypertrophies in order to normalise afterload. In the OxVALVE study however, there was no statistically significant association between a diagnosis of AS of any severity and LV mass or mass index. This is a result of having small numbers of participants in the study who were found to have aortic stenosis. Only 32 participants (1.3%) were diagnosed with aortic stenosis in the study, of which nearly half were mild AS.

The data presented here demonstrate a significant association between a diagnosis of aortic regurgitation and LV mass and mass index. Eccentric and concentric hypertrophy occur in AR along with LV dilatation, to support an increase in total stroke volume from the LV(111, 112). The OxVALVE data also demonstrate that LV mass index increase with increasing severity of AR. This agrees with data from Padial et al, who demonstrated the greatest increases in LV mass in those with more severe AR(110). An increase in left ventricular mass has also been shown to be associated with poorer surgical outcomes in those with AR(241).

In mitral regurgitation, left ventricular dilatation occurs to compensate for the increased loading of the left ventricle. This dilatation results from addition of sarcomeres as well as their rearrangement(141, 142), resulting in increased left ventricular mass. The finding of increased LV mass in MR of all levels of severity suggests that this compensation may begin at an early stage of valvular dysfunction.

Although studies have looked at LV mass in outcomes of AS(74, 79-82), this is less well studied in valvular regurgitation. Enriquez-Sarano did not demonstrate an association between LV mass and outcomes in mitral regurgitation, but did show an increase in LV mass with increasing size of the regurgitant orifice(208). Similar findings were observed in AR patients by Detaint et al(208), with increasing mass associated with increasing severity of AR in the absence of any independent effect on outcomes.

3.12.7 Costs of screening for VHD in OxVALVE

The cost of screening for VHD in this study was approximately £79.00 per participant recruited. This cost includes room hire, administrative and staff costs, as well as consumables, but excludes the cost of the echocardiography machine. This equates to a cost of approximately £155.50 per patient newly diagnosed with VHD. When considering just those with moderate or severe VHD detected at screening, the cost rises significantly to £1234.40. However, the costs of leaving significant VHD undetected may be higher still. Looking at the costs associated with hospitalisation due to aortic valve disease alone in the first decade of this century, Badheka et al demonstrated a significant increase(242). The cost of a hospitalisation due to aortic valve disease in a patient over the age of 60 yrs increased from $31,909 to $38,172 between 2000 and 2012. Extrapolating from these figures, the authors predict that the total cost of hospitalisation due to aortic valve disease in the United States will reach nearly $3 billion by 2020. Within the UK, Berry et al demonstrated a trend towards increasing hospitalisations due to aortic valve disease between 1997 and 2005(16). This suggests that a similar impact could be seen on the UK healthcare budget, with significant ramifications for resource management. Screening for VHD may allow more timely detection of significant lesions, thus permitting surveillance with prompt

intervention if required. Avoiding costly acute admission, in particular for heart failure, may justify the expenditure on screening.

3.13 Conclusions

Echocardiographic screening for VHD in a community-based setting demonstrates a high prevalence of previously undiagnosed VHD, although most is mild. The prevalence of VHD increases significantly with age, as does the likelihood of moderate or severe VHD. Mitral and aortic regurgitation are the most commonly detected forms of VHD.

Female gender, atrial fibrillation, and lower body mass index are positively associated with a finding of mitral regurgitation. Current smoking status is associated with a increased likelihood of aortic stenosis.

The finding of a significant prevalence of VHD in this expanding part of the population should add impetus to the search for better interventions (medical, surgical, percutaneous), improved methods of prognostication (imaging, genetic, biomarkers), and optimal detection and surveillance strategies. Investment in this may offset the morbidity and mortality currently seen with untreated severe valvular heart disease, and prove to be cost-saving in the longer term.

3.14 Limitations

This study had a response rate of 52% amongst those invited to participate. Although this is a high response rate in this setting, and within the constraints set by the Ethics Committee, there is the potential for those patients who are highly motivated and healthy, with fewer co-morbidities, to be represented; this would perhaps lead to an under-estimate of the prevalence of VHD by the study.

The proportion of participants in each age band is higher in the younger age groups compared with the wider Oxfordshire population, and also the population of England and Wales. This reflects the level of frailty and co-morbidity amongst older invitees

who declined to participate. As the prevalence of VHD increases with age, and a previous diagnosis of VHD was an exclusion criterion, a higher proportion of potential invitees in the higher age bands will have been excluded on this basis. Despite these factors, the results demonstrate a significant increase in the prevalence of VHD with age, and if anything is likely to underestimate the prevalence of undiagnosed VHD in the age group studied.

A lack of ethnic diversity may also affect the results of this study. The overwhelming majority (98.8%) of participants in this study classed themselves as white. Although this is a good representation of the Oxfordshire population in the same age range (98% white), the broader UK population is more ethnically diverse than this. Table 3.13 shows the breakdown of ethnic groups in the OxVALVE participants, the Oxfordshire population, and the population of England and Wales in UK residents aged 65 years and older(17). Compared with the wider Oxfordshire population, the proportion of study participants from a non-White ethnic background was slightly lower across most groups, with the exception of participants from a mixed ethnic background. This difference is also reflected in the comparison of study participants to the population of England and Wales, again with the exception of mixed ethnic residents.

In order to address the disparity in ethnic diversity between study participants and the wider population, the choice of study sites took in to account the population served by the site. Sites were chosen with the intention of providing the covering broadest cross-section of ethnic and socio-economic possible. In addition, approval was sought from the Ethics Committee to engage with advocates within minority groups. Unfortunately this request was not approved, and it was not permitted to approach specific sectors of the community to increase engagement with the study. Study sites for the ongoing data collection of the study have also been targeted at areas with more diverse ethnic populations, as well as a broader socio-economic composition of the population.

Table 3.13 Comparison of ethic origins of OxVALVE participants with Oxfordshire population and population of England and Wales

	OxVALVE participants	Oxfordshire population	Population of England and Wales
White (British, Irish, other white background)	98.8	97.8	95.5
Asian/Asian British	0.6	1.1	2.6
Mixed/multiple ethnic group	0.4	0.3	0.4
Black/African/Caribbean/Black British	0.1	0.6	1.3
Other	0.1	0.1	0.3

Results are expressed as percentages. N=2500 for OxVALVE participants.
Data for Oxfordshire population, and population of England and Wales taken from Office of National Statistics National Census 2011 data.

It is possible that the recruitment of participants from other ethnic groups may affect the levels of rheumatic valve disease seen, as rheumatic valve disease remains a significant health care problem in less developed countries(6, 7). Epidemiological studies in the United States have had a broader ethnic range, and have reported comparable prevalences to those found in this study, when taking in to consideration differences in inclusion criteria.

Aortic stenosis has been shown to be associated with vascular risk factors, including factors associated with vascular calcification. Reduced bone mineral density has been demonstrated to be associated with aortic valve calcification and aortic stenosis(65, 243, 244). This has raised the possibility that treatment for osteoporosis, such as bisphosphonates and denosumab, may help to slow or reverse the progression of AS. There is some evidence to support this from smaller studies(245, 246), and there is a randomised trial in progress to look at this further(247). The most commonly prescribed anticoagulant therapy, warfarin, has also been linked with vascular calcification and also calcification of the aortic valve(248-250). Although some data on the use of anticoagulation and additional medication was collected in the OxVALVE study, these data are incomplete. Data on whether or not participants had

been diagnosed with osteoporosis were also not captured by the study. The availability of such data would have provided the potential to look further at these factors in participants with and without aortic stenosis. This may be a target for future areas of study within the OxVALVE cohort in future. However, the study was established with a view to looking at all forms of VHD, and not simply aortic valve disease, hence the lack of robust data in these areas.

Chapter 4: Provocation of anxiety, and attitudes to screening for valvular heart disease

4.1 Introduction

In order to increase detection and intervention rates for VHD, data defining the scope of the problem are needed, and screening programmes must be considered. In 1968, principles for the evaluation of screening programmes were published by Wilson and Jungner, for the World Health Organisation(251). In essence, these say that an ideal screening test should be a safe, minimally-invasive, and cost-effective procedure that has a high sensitivity and specificity, and is easily administered, preferably in a community setting. It should identify a clinically significant condition, that will cause significant morbidity and mortality if left untreated. The condition being screened for should also have a pre-symptomatic phase during which the disease can be detected, and should have an accepted form of treatment. In the case of our study, VHD is a clinically significant condition, which may result in morbidity and mortality if timely surgical intervention is not undertaken, and the cost to healthcare of managing this is significant. Transthoracic echocardiography is safe, non-invasive and cost-effective, and modern compact portable machines permit widespread community-based use. In experienced hands, it has an excellent sensitivity & specificity for the detection of VHD. Community-based echocardiographic programmes for screening for VHD would therefore seem to fit with the Wilson and Jungner principles for screening.

Alongside this however, should also be the consideration of the possible harm which might be experienced by those being screened, particularly those who are found to have a false negative result. There has been much debate over the potential psychological impact of screening(252, 253), with concerns being raised about the potential for significant anxiety to be caused by such programmes, and the

acceptability of echocardiography in this setting have not previously been assessed. An assessment of these was therefore included within the OxVALVE study.

4.2 Study questionnaires

4.2.1 Completion of questionnaires

At the end of visit 1, participants were asked to complete a study questionnaire. This consisted of two sections: the first part was the short form of the Spielberger State-Trait Anxiety Inventory (STAI) to assess levels of anxiety provoked by participation in the study, and the second part was formulated to assess participants attitudes to screening for VHD. A copy of the full questionnaire is found at Annex A.

Completion of the questionnaires was mostly undertaken independently by participants, in the GP waiting area, in order to avoid possible bias in responses. However, when participants required assistance of study staff to complete the questionnaire, this was provided.

4.2.2 Spielberger State-Trait Anxiety Inventory questionnaires

The Spielberger State-Trait Anxiety Inventory is a well-validated and widely-used measure of anxiety in applied psychology research(254). The full STAI consists of 40 individual questions, and therefore is time-consuming to complete. However, a short form has been developed and validated(219), and has been used in similar settings to the OxVALVE study, in order to determine levels of anxiety provoked by screening(255). The short form consists of just six questions, with four or more responses sufficient for a meaningful result.

Data from the STAI responses were input with inversion of the values from questions 1, 4 and 5, as per the developers' guidelines. Scores were then prorated, with a score of 42 or more representing clinically significant anxiety.

4.2.3 Attitudes to screening

The second section of the survey assessed participants' attitudes to screening and to the study delivery itself. This served two purposes: firstly it permitted adjustments to the way in which invitations to participate and study information were formulated and distributed if responses indicated dissatisfaction with the original methods; and secondly, it gave an insight into whether participants considered screening for VHD in general, and using echocardiography specifically, to be important and acceptable. This second aspect is of particular importance in the consideration of widespread screening for VHD.

This section of the questionnaire was developed in collaboration with staff in the Department of Primary Healthcare of Oxford University. It was based on questionnaires used in research into screening for colorectal cancer(256), and asked questions to determine:

- whether participants were aware of the programme prior to receiving an invitation to participate;
- whether they found receiving a postal invitation to be satisfactory;
- whether they would have preferred to have been offered the opportunity to participate when visiting the practice for another reason;
- how important they considered healthcare screening in general; how important they considered screening for VHD;
- whether they felt that the invitation letter explained the programme satisfactorily;
- whether they would have echocardiography for VHD screening again.

With the exception of responses relating to prior awareness of the study, answers were given on a five-point scale, with 1 representing Definitely Not/Not Important and 5 representing Definitely Yes/Very Important.

Appendix 1 is the full B2 questionnaire, which contains the short STAI section and attitudes to screening questions, as provided to participants of the study.

4.3 Results

4.3.1 Study population

Of the first 2500 participants enrolled in the OxVALVE study, 2186 appropriately completed and returned the short STAI section of the questionnaire, and 2361 completed the questions on attitudes to screening. A minimum of four out of six responses was required for completion of the STAI. The characteristics of questionnaire respondents are presented in Table 4.1.

Table 4.1 Characteristics of questionnaire respondents

Short STAI questions (N=2186)		
Age, mean (SD)	72.4	(6.0)
Gender	**N**	**(%)**
Male	1060	(48.5)
Female	1126	(51.5)
New diagnosis of VHD		
Yes	929	(42.5)
No	1257	(57.5)
Attitudes to screening questions (N=2361)		
Age, mean (SD)	72.9	(5.90)
Gender	**N**	**(%)**
Male	1138	(48.2)
Female	1223	(51.8)
New diagnosis of VHD		
Yes	975	(41.3)
No	1386	(58.7)

4.3.2 Statistical analysis

Participants were stratified by age, gender, and presence or absence of VHD to explore the prevalence of clinically significant anxiety scores in the study population. As not all of the first 2,500 participants of the OxVALVE study completed the questionnaires, summary statistics are presented for each of the questionnaires. Clinically significant anxiety levels are indicated by a score greater than 42. The chi-square test or the Fisher's exact test were used to compare discrete data as appropriate; and non-parametric testing was carried out using the Mann-Whitney and Kruskal Wallis tests. The factors associated with a clinically significant anxiety score were assessed, and the chi-square test was also used to look at the association of a new diagnosis of VHD with a clinically significant score on the STAI questionnaire.

4.3.3 STAI questionnaire

Of the first 2500 participants recruited to the study, 2186 (87.4%) appropriately completed the STAI questionnaires. Out of these 2186, 5 participants (0.23%) answered 4 STAI questions, 26 participants (1.19%) answered 5 STAI questions, and 2155 participants (98.58%) completed all six of the STAI questions. 223 respondents (10.2%) had a score >42, indicating a significant level of anxiety. Those with a significant anxiety score were more likely to be female than male (13.04% and 9.05% respectively, $p<0.001$). Participants who received a new diagnosis of VHD were also more likely to have a STAI score >42, compared with those who were not found to have VHD (12.7% compared with 8.4%, $p<0.001$). There was no association between age and anxiety score. These results are shown in table 4.2 and 4.3.

Table 4.2 Association of gender, and new diagnosis of VHD with STAI score

STAI score	Male	Female	P value	VHD -	VHD +	P value
≤42	975 (92.0)	987 (87.7)		1151 (91.6)	811 (87.3)	
>42	85 (8.0)	138 (12.3)	0.001	105 (8.4)	118 (12.7)	0.001

All values are expressed as numbers (%); p-value <0.05 was considered significant

Table 4.3 Association of STAI score and age

STAI score	65-69	70-74	75-79	80-84	≥85	P value
≤42	785 (90.0)	544 (89.6)	352 (87.6)	202 (94.0)	80 (88.9)	
>42	87 (10.0)	63 (10.4	50 (12.4)	13 (6.0)	10 (11.1)	0.78

All values are expressed as numbers (%); p-value <0.05 was considered significant

4.3.4 Attitudes to screening questions

The first 2500 enrolled participants of the study yielded 2361 (94.4%) appropriately completed questionnaires on attitudes to screening. Only 21.5% of responders had heard of the study before they received their invitation to participate. 95.4% were satisfied with having received a postal invitation to participate, while 6.2% would have preferred to receive their invitation when visiting the surgery for another reason. The initial invitation letter was felt to explain the tests clearly by 96.5%, while only 0.5% felt that it did not explain the tests clearly.

Health screening in general was felt to be important or very important by 97.2%, but was classed as not important or slightly important by 1.4%. On logistic regression, there was no association between age, gender or a new diagnosis of VHD and a positive attitude to the importance of health screening in general.

When asked specifically about screening for VHD, it was rated as important or very important by 95.9%, while 1.3% considered it to be slightly/not important, as demonstrated in Figure 4.1. There was no significant difference in gender, age, or a new diagnosis of VHD amongst those who had a positive attitude towards screening for VHD, when compared with those who did not express a positive attitude.

When asked whether they would be prepared to have the same test again, 98.5% responded yes or definitely yes; only 0.3% indicated that they would not undergo the screening test again, and 0.9% were unsure. There was no association between gender or a new diagnosis of VHD, and a willingness to undergo echocardiography again on logistic regression. However, age was strongly associated with whether or not a participant would be willing to undergo echocardiography again. Those who were older were less likely to express a willingness to undergo echocardiography in the future (OR 0.93; 95% CI 0.88,0.98; p=0.008).

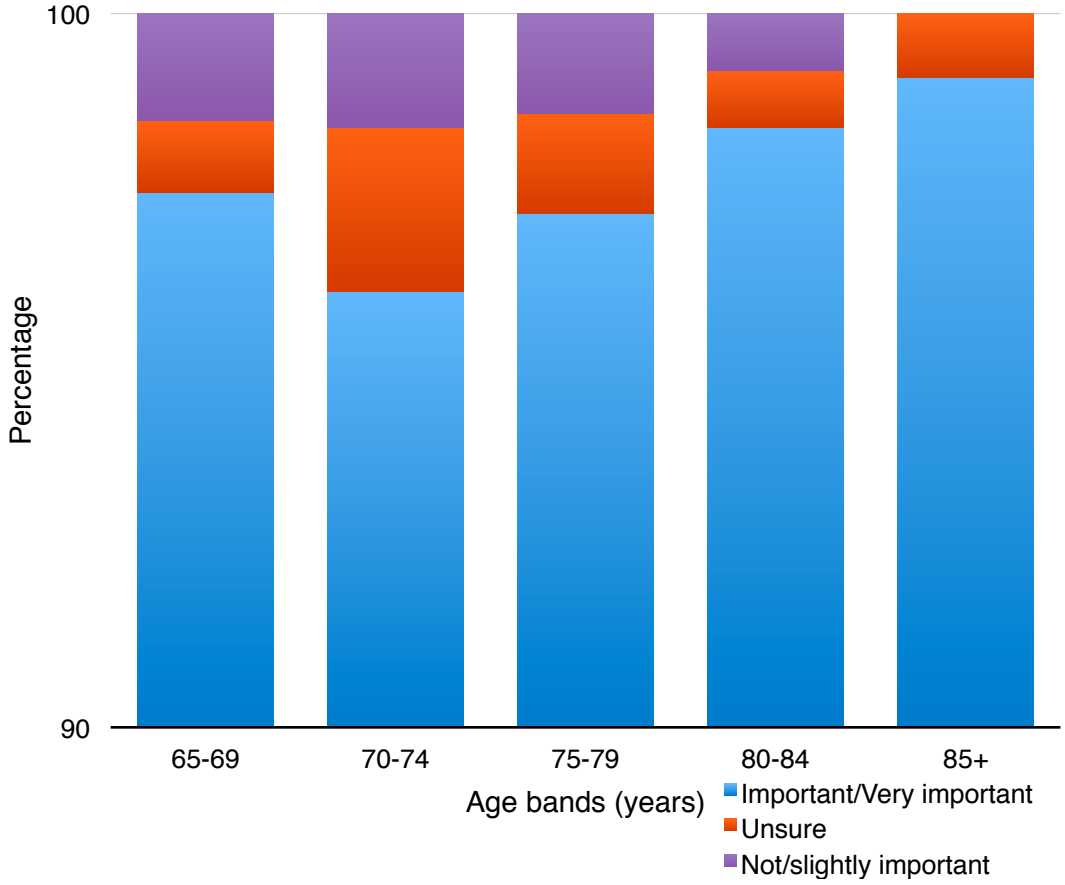

Figure 4.1. Attitudes to the importance of screening for VHD by age band

4.4 Discussion

These results demonstrate that in a community-based echocardiographic screening programme for VHD:

1) A clinically significant level of anxiety are provoked only in a small number of participants, and is related to gender and diagnosis of VHD.

2) Attitudes towards such a screening programme are positive, and the test is highly acceptable to patients.

4.4.1 Levels of anxiety provoked in screening for VHD in the community.

Only a minority of participants (10.2%) indicated that the screening programme provoked clinically significant levels of anxiety, based on a score in excess of 42 on the short form of the Spielberger State-Trait Anxiety Inventory. This compares favourably with other studies looking at anxiety associated with screening programmes(39, 255, 257). The immediate availability of the results of screening may well play a role in this, as it has been shown that being given a result at the time of screening is more reassuring than having to wait(258). It might be expected that those with health-related anxiety might be more likely to accept an invitation for screening, in which case high levels of self-reported anxiety might be expected. The low levels of anxiety expressed by participants in our study, however, would seem to suggest that this may not be the case.

The association of increased anxiety levels with gender has not been previously explored in connection with screening programmes, and does not have any obvious explanation. Female participants may feel more comfortable admitting to personal levels of anxiety than male participants, or the physical exposure associated with undergoing echocardiography may be more anxiety-provoking for women in this age group than their male counterparts.

Although intuitively the finding that a new diagnosis of VHD on screening is significantly associated with higher levels of anxiety seems unsurprising, the findings of Lucarotti et al in abdominal aortic aneurysm screening do not support this(259). However, it does agree with findings of other screening studies, which have demonstrated that being given a negative result from screening provides greatest reassurance(260-262). Although higher than those in the screen-negative group, anxiety levels were still low in the screen positive group (12.7%), which suggests that delivering results at the point of screening, and assurances by the study team that follow up arrangements would be put in place, may well have helped to alleviate participants' concerns.

The timing of completion of the STAI questionnaire may be a factor in the finding of higher levels of anxiety in those with a new diagnosis of VHD. Participants who were informed that they had no VHD shortly before completing the STAI might have reflected this recent reassurance by reporting lower levels of anxiety than they would have reported prior to echocardiography. The opposite might be true for those receiving a new diagnosis of VHD. Screen positive participants were provided with a printed study leaflet, which explained what the results might mean for the participant, and outlined the likely future course of follow up, both within the study and potentially in out-patient clinics. However, at the time when participants were completing the STAI questionnaire at the study visit, they would not have had the opportunity to read the leaflet, and experienced any reassurance from receiving this information.

4.4.2 Attitudes and acceptability in a VHD screening programme

The relatively low levels of awareness of the screening programme amongst those being screened is not surprising in the context of a relatively small programme, operating relatively locally. Methods of publicising the study included placing posters in participating GP surgeries, and advertising the study on display screens in the surgeries; leaflets were also left on tables in the waiting rooms of participating practices. Despite the relatively small percentage of participants who were aware of the study prior to receiving their invitations, our uptake rate for the study was still good.

The majority of participants expressed positive attitudes towards screening in general, and a very high percentage (94.2%) also expressed positive attitudes towards screening for VHD specifically. Marjoram et al found similarly positive levels in a small group of patients being offered screening for bowel cancer(256), and even in patients who have been found to have false positive results, Mant et al reported reported positive attitudes to screening(263).

Acceptability of echocardiography in the community to screen for VHD was also very high. When asked whether they would be willing to have the screening test again, 98.7**%** of participants answered either "Yes" or "Definitely yes", as opposed to only 0.3% who replied "No" or "Definitely No". This is significantly higher than that suggested by a study into compliance rates of those offered faecal occult blood testing for bowel cancer, reported by Hobbs et al(264), and is comparable to the high levels of acceptability reported by other screening studies(255, 263, 265). This is likely to be related to the non-invasive and non-painful nature of echocardiography, although it does require patients to expose their torso, which might be expected to be less acceptable for female patients.

4.5 Limitations

The main limitation of assessing anxiety and acceptability in this cohort, is that participants self-selected by either accepting or declining the invitation to participate. How this will potentially bias the findings is not clear as those who accept the screening invitation may have more baseline health concerns than those who don't accept the invitation, and may have higher anxiety scores as a result; conversely, those with the highest levels of anxiety about screening may decline the invitation because of this, resulting in lower overall anxiety scores. Although obtaining data on anxiety from non-respondents is likely to prove challenging, and in our study would not have been permitted by the ethics committee, an assessment of pre-test anxiety levels may give an indication as to whether the screening experience itself influences anxiety levels for individuals. These data have been obtained for those who chose to participate in our study, and analysis of these data may be informative in this area.

The STAI responses are also based on anxiety levels at a single point in time, and other studies have demonstrated changes in anxiety levels - both increasing and decreasing - in screening participants, when anxiety was assessed at least a month after the initial anxiety assessment(39, 259). Understanding whether screen-positive subjects have persistently raised levels of anxiety may allow interventions to alleviate this, and should stimulate further study of which particular factors cause psychological distress to this patient group.

The questionnaire was completed during the study visit, shortly after the participant had undergone echocardiography, and had been given the results of echocardiography. The timing of completion may have influenced the participants' responses, and may be a factor in the finding of higher levels of anxiety in those with a new diagnosis of VHD. Although participants were provided with a leaflet explaining the diagnosis to them, they would not have had the opportunity to read this prior to completing the questionnaire, and anxiety levels may have been higher in these participants after their echo study had been performed than prior to it. Conversely, those who were informed that they had no VHD may been reported lower levels of anxiety by completing the questionnaire after receiving their results than if it had been completed prior to the echo. As the STAI questionnaire was incorporated into the same document as the questions on attitudes to screening, it was completed after echocardiography had been performed. This allowed participants to reflect their experience of echocardiography as a screening tool, and how acceptable they had found it. The two sections of the questionnaire could be completed at separate timepoints within the study visit, although this would affect the length and flow of the visit.

A second STAI questionnaire was sent out to participants three months after their study visit, to assess how anxiety levels changed over time. Although these data have been collected, they are not currently available.

A further limitation of this study is that data were not collected on specific mental health diagnoses. It may be the case that those who reported higher levels of anxiety had a pre-existing diagnosis of mental illness, which could have been the reason they felt anxious rather than because they were participating in the study. However, in those participants with a diagnosis of mental illness, particularly those with anxiety-related disorders, medication used to treat the condition might have meant that they reported lower levels of anxiety. Mental illness may also have been undiagnosed in a proportion of participants, and this would possibly have affected their responses to the STAI, and they would not have been benefiting from receiving treatment for mental illness.

The use of antidepressants in participants may have provided an indicator of those more at risk of anxiety. Although participants were asked for complete data on their medication history, these data were not complete. Some medications which might be used as antidepressants or anxiolytics may also be used for other purposes, such as the use of amitriptyline for neuropathic pain or benzodiazepines for sleep disorders; some anxiety-related disorders might be treated with medication other than antidepressants, such as propranolol. Therefore the data available were not sufficiently robust as to be analysable in this context. A history of antidepressant or anxiolytic drug use could also have confounded results on anxiety. Participants who were taking such medications might have actually experienced comparable levels of anxiety to those not taking them as a result of the treatment. The variety of medications used to treat anxiety and depression is very broad, and the potential for confounding considerable and therefore these data cannot be considered to be robust in this context.

4.6 Conclusions

In a large cohort of elderly subjects, community-based echocardiographic screening for VHD does not provoke significant levels of anxiety, although clinically significant anxiety scores are more common among women and those found to be screen-positive. Attitudes towards health screening in general, and screening for VHD in particular, are positive. Echocardiography as a screening test for VHD is highly acceptable to patients.

Chapter 5: Cardiac magnetic resonance for predicting outcomes in mitral regurgitation

5.1 Introduction

The optimal timing of surgery in mitral regurgitation remains a source of discussion, with the risks of early surgery, and possibility of valve replacement rather than repair, being weighed against the possibility of irreversible myocardial damage if severe regurgitation remains untreated for too long. Quantitation of mitral regurgitation using echocardiography has been shown to relate to outcomes(12, 171), but semi-quantitative methods are more commonly used in routine clinical practice. CMR can quantify mitral regurgitant volume and fraction, using phase-contrast velocity mapping and measurement of left ventricular volumes and systolic function. Trans-aortic flow measured in this way has been shown to correlate with in vivo and in vitro stroke volume measurements(266-269), and CMR is regarded as the 'gold standard' for measurement of LV volumes. The indirect calculation of mitral regurgitant volume by subtraction of aortic flow from LV stroke volume optimises inter- and intra-observer variability(202), and also allows the potential to correct for co-existent aortic regurgitation. Trans-thoracic echocardiography is the most widely used tool for the longitudinal assessment of valvular heart disease, including mitral regurgitation. Its relatively low cost, lack of ionising radiation, and non-invasive nature make it an ideal tool for this. However, quantitative parameters for the grading of MR severity rely on optimal image quality, in the presence of central jets through non-elliptical regurgitant orifices in order to optimise accuracy; this combination of qualities is not always present in the real-world patient population.

In this chapter, the utility of quantitative CMR assessment of MR to predict outcomes is considered. A comparison study of MR quantitation using the PISA method and two-dimensional trans-thoracic echocardiography is also presented.

5.2 General methods

5.2.1 Subject recruitment, inclusion and exclusion criteria

Asymptomatic patients with primary mitral regurgitation of greater than mild severity (according to established echocardiographic criteria(22)), with no other indications for mitral surgery, were identified from 4 high-volume CMR centres, three in the United Kingdom (Oxford, Leeds, and Royal Brompton Hospital, London) and one in New Zealand (Aukland). In Oxford, patients participated in a research study, as described below, with annual CMR scans; decisions on clinical management were made without knowledge of the results of CMR scans. In the other three centres, study patients were identified from the clinical databases of CMR studies, and CMR scan results were available to clinicians. Asymptomatic patients, with no other indications for mitral valve surgery, were recruited in order to allow longitudinal follow up, and to avoid the potential bias of patients undergoing a CMR scan with surgery already planned. This patient group is of particular interest, as predictors of progression to surgical intervention, and the optimum time for that intervention to take place, remain unclear. Patients were followed for up to 8.2 years; those who remained asymptomatic and were managed conservatively are described as the conservative group, and those who became symptomatic or reached thresholds for surgical intervention are described as the crossover group. In the crossover group, the point of censoring is the point at which decisions about surgery were made. All decisions on clinical management were made by the treating physician.

Subjects were eligible for inclusion in the study if they fulfilled the following criteria:

- Aged 18 or above
- Had provided informed consent
- Had asymptomatic mitral regurgitation of greater than mild severity on echocardiography

Subjects were excluded from participating if any of the following applied:

- Any other significant (>mild) valvular heart disease

- Any contraindications to CMR scanning (pacemakers, implantable defibrillators, other metallic implants)
- Evidence of significant coronary artery disease

As the sizes of the two groups (conservative and crossover) and the survival outcomes were also unknown, a power calculation was not undertaken before recruitment commenced. A post-hoc power calculation using the actual survival and group sizes using the cut-off for regurgitant volume was therefore undertaken. Using surgery- or symptom-free survival of 91% and 21% for a regurgitant fraction of ≤55ml/beat and >55ml/beat respectively, with 85% power (β error) and 95% confidence (α error), the total sample size required is 49. The total sample size for the study presented here was 109 participants.

Those participants recruited in Oxford who were included in the sub-study described in section 3 of this chapter, were prospectively recruited from November 2009 to April 2011 from outpatient clinics at the John Radcliffe Hospital and surrounding hospitals in Oxford. Each participant gave written, informed consent to participate in the study, which was approved by the Central Oxfordshire Research Ethics Committee (C02.020).

5.2.2 CMR scanning

All patients were scanned on 1.5T scanners (Siemens Avanto [Siemens Medical Solutions, Erlangen, Germany] or Philips Achieva scanners [Philips Healthcare, Best, The Netherlands]. Subjects underwent ECG-gated scanning, which measured:

- right and left ventricular volumes and function
- left ventricular mass
- aortic valve flow.

Scans were analysed in each centre using the manufacturer's software (Siemens Argus and Philips ViewForum respectively), to measure volumes and flow.

5.3 CMR and 2D TTE sub-study methods

5.3.1 Subject recruitment, inclusion and exclusion criteria

Subject recruitment, and study inclusion and exclusion criteria are as described in section 2.1 of this chapter.

5.3.2 Clinical assessment

On the day of scanning, all participants completed a clinical assessment. A focussed medical history was obtained, and the following were documented:

- The presence or absence of any exclusion criteria
- The presence or absence of cardiovascular symptoms, with particular attention to shortness of breath, palpitations, and ankle swelling
- Assessment of New York Heart Association class
- Current medications

The following physical measurements were also recorded:

- Height (cm)
- Weight (kg), using calibrated scales
- Blood pressure (using an automatic sphygmomanometer, Omron M6 blood pressure monitor, Kyoto, Japan)
- Pulse rate and rhythm

Participants then underwent transthoracic echocardiography and a cardiac magnetic resonance scan on the same day.

5.3.3 Echocardiography scan protocol

Trans-thoracic echocardiography was performed using a Philips iE33 advanced echo system (Philips Medical Systems, Best, Netherlands), equipped with 2-5-3.5Mhz transducers.

A full echo study was performed according to the European and American Society for Echocardiography guidelines for the assessment of native valvular regurgitation(33), and chamber quantification(270). Left ventricular volumes and ejection fraction were calculated according to Simpson's rule.

Assessment of the regurgitant flow was calculated from the proximal isovelocity surface area (PISA). PISA was measured by obtaining optimal images of the mitral valve in the apical 4-chamber view with colour flow mapping displaying the regurgitant jet at the Nyqvist limit at 40cm/s. Radius of the PISA was used to calculate regurgitant flow, according to the formula:

$$\text{Regurgitant flow} = 2\Pi r^2 \text{ x aliasing velocity}$$

where r is the PISA radius.

5.3.4 CMR imaging scan protocol

All scanning was performed on a Siemens 1.5T Avanto MR system (Erlangen, Germany), with scans lasting approximately 30-35 minutes. Subjects underwent a CMR scan protocol which measured the following:

- Cardiac function and left ventricular mass
- Aortic valve flow, using standard through-plane breath-hold sequences

5.4 Cardiac mass, volumes and function

CMR Steady-State Free Precession (SSFP) sequences are well established as an accurate, reproducible and valid method for the measurement of left ventricular volumes and mass(192-195). Pilot images, horizontal and vertical long axis images, and a short axis stack were acquired for the calculation of cardiac volumes and function, with participants in the supine position, as per standard CMR protocols(271). Slices were 7mm thick, with a 3mm gap, and images were acquired during a breath-hold at end-expiration to minimise the effects of respiratory motion on image quality. Images were retrospectively gated for patients in sinus rhythm, and prospectively triggered for patients in atrial fibrillation.

Epicardial and endocardial borders were manually contoured using the manufacturers' software, in order to calculate end diastolic volumes (EDV), end systolic volumes (ESV), stroke volumes (SV), ejection fraction (EF) and myocardial mass.

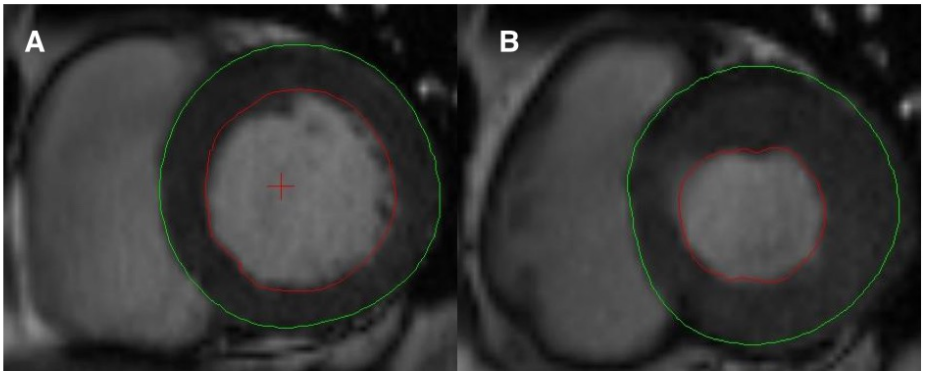

Figure 5.1 Measurement of LV volumes and ejection fraction.
LV contoured in diastole (A) and in systole (B).

5.5 Aortic flow assessment

Aortic flow (Ao flow) was measured using through-plane phase-contrast velocity mapping, which is accepted as a reproducible CMR technique for quantification of flow. Left ventricular outflow tract (LVOT) and coronal LVOT images were obtained, and an image slice for the flow sequence was placed perpendicular to the direction of flow in the aortic root, just above the valve at end diastole. The majority of patients were imaged using breath-hold sequences were used to acquire data within a single breath-hold (12-16 heartbeats); one centre routinely used non-breath-hold sequences. All sequences were acquired with the region of interest at the isocenter of the magnet, in order to minimise any inhomogeneities in the magnetic field, which might give rise to background flow offset errors.

From the resulting flow images, using the manufacturers' software, a region of interest in the aortic root was defined and flow was measured by integrating the flow

in each frame over a single cardiac cycle, as previously described(272). Regurgitant volume (RVol) was calculated as LVSV - Ao flow (ml); regurgitant fraction (RFrac) was calculated as (RVol/LVSV) x 100 (%).

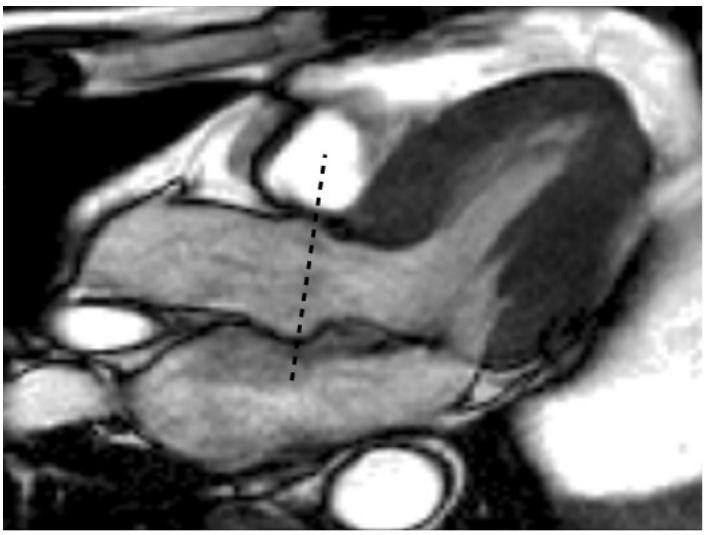

Figure 5.2 Position of imaging plane for CMR measurement of aortic valve flow

5.6 Clinical follow up

Follow up information came from examination of hospital records. Those who developed symptoms, or reached other indications for surgical intervention, were censored at the point at which surgical intervention was considered. Participants who did not meet these criteria were censored at last clinic visit occurring during the study period. The clinical management of participants was independently decided by the treating clinicians. Events were only counted if the reason for mitral valve surgery was for established indications(22), which do not include CMR assessment.

5.7 Statistical analysis

T-tests were used to compare parameters between the two groups. Receiver operating characteristic curve (ROC) analysis was used to determine the ability of parameters to discriminate between those patients who would develop symptoms or other recognised indications for surgery, and those who would not. Differences in ROC area were compared using the method of DeLong et al(273). Kaplan-Meier curves were generated to demonstrate associations with progression to symptoms or indications for surgery. All analyses were performed with SPSS version 20 (SPSS Inc, IL), except for the ROC analyses, which were performed on MedCalc version 14.12.0 (MedCalc Software, Mariakerke, Belgium). Results are expressed as mean±standard deviation, and a p-value of <0.05 was considered significant.

5.8 Main study results

5.8.1 Study population characteristics

One hundred and nine patients with asymptomatic MR of more than mild severity, were included in the study. They were followed up for up to 8.2 years (mean 2.3 yrs). Participant demographics are presented in Table 5.1. The mean age of participants was 65 years (range: 24-86), and 35 patients were female. There was no significant difference in characteristics of patients in the two groups at baseline.

Table 5.1 Patient Demographics

Patient characteristics	**Conservative Group** (N=84)	**Crossover Group** (N=25)	**P value**
Age, mean (range)	65.18 (24-86)	63.75 (30-86)	0.664
Male, n (%)	74 (80.66)	19 (76.00)	0.327
BSA, m2	1.88±0.18	1.89±0.24	0.821
Symptom status			
NYHA I, n (%)	68 (80.95)	17 (68.00)	
NYHA II, n (%)	5 (5.95)	5 (20.00)	

Table 5.1 Patient Demographics

NYHA III, n (%)	2 (2.38)	1 (4.00)	
NYHA IV, n (%)	0 (0.00)	0 (0.00)	0.115
Haemodynamics			
Heart rate, bpm	68±13	67±10	0.778
Atrial fibrillation, n (%)	16 (19.05)	8 (32.00)	0.173
Systolic BP, mmHg	144±23	132±20	0.87
Diastolic BP, mmHg	78±11	77±9	0.908

Values expressed as mean±SD, unless otherwise indicated; p value <0.05 was considered significant; BSA: body surface area; NYHA: New York Heart Association class; BP: blood pressure

5.8.2 Cardiac magnetic resonance

Volumetric and flow data were available for all patients. Results are displayed in Table 5.2. Volumetric indices (LVEDV and LVESV), and their indexed values, were significantly higher in those in the crossover group. Ejection fraction was not significantly different between the two groups (p=0.84), suggesting that these patients had not developed significant LV systolic dysfunction as a result of their mitral valve disease. As might be expected, quantitative CMR measures of mitral regurgitation (regurgitant volume and fraction) were significantly lower in those in the conservative group, compared with those progressing to surgery (p=<0.001 for both parameters).

Table 5.2 CMR data

CMR data (N=109)	Conservative Group (N=84)	Crossover Group (N=25)	p-value
LVEDV, ml	183±50	224±48	<0.001
LVEDV index, ml/m^2	98±25	118±23	0.001
LVESV, ml	62±26	82±29	0.002
LVESV index, ml/m^2	34±14	43±13	0.005
LVEF, %	67±8	64±7	0.84
Regurgitant volume, ml	39±20	66±24	<0.001
Regurgitant fraction, %	32±12	46±12	<0.001

Values are expressed as mean±SD, in the units indicated. LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction

5.8.3 Predictors of progression to symptoms or surgery

During the follow up period, 25 (22.9%) patients underwent mitral valve surgery for symptoms (n=9) or established indications for surgery (reduced LV systolic function [<60%] on echo, LV dilatation [LVESD>45mm], onset of atrial fibrillation, pulmonary hypertension [pulmonary artery systolic pressure >50mmHg with no other cause]). Mean time from CMR scan to surgery was 23 months, median was 1.1 years.

Receiver-operator characteristic (ROC) analysis showed that quantitative measures of MR on baseline CMR scans had good discriminatory power. The AUC for mitral regurgitant volume was 0.81 (P<0.0001; 95% CI: 0.721;0.877). Using a cut-off value of >55ml/beat, it has a good sensitivity (72%) and high specificity (87%) for identifying those who progressed to symptoms or surgery. Regurgitant fraction for MR was only slightly less discriminating, with an AUC of 0.79 (P<0.0001; 95%CI: 0.699;0.860). A cut-off value of 40% has a sensitivity of 76%, and specificity of 74%, for identifying those progressing to surgical indications. The use of higher

thresholds for regurgitant fraction can allow prediction of progression with an even greater degree of certainty; when a cut-off value of 50% RFrac is used, the specificity increases to 92%, although with a lower sensitivity (40%).

In order to examine the effect of time on progression to symptoms/surgery, Kaplan-Meier survival curves were generated, using the discriminator values identified on ROC analysis. For both regurgitant volume and regurgitant fraction, there was significant separation of the groups with time (see Figures 5.3 & 5.4). For those patients with regurgitant volume ≤55ml/beat, survival without surgery at the median time point (1.1 years) was 95%. In those with a regurgitant fraction >55ml/beat, survival without surgery at the same time point was only 69%. Similarly, when using a cut off value of 40% for regurgitant fraction, survival without surgery is 94% for those with a regurgitant fraction ≤40%, compared to 79% for those with a regurgitant fraction >40%.

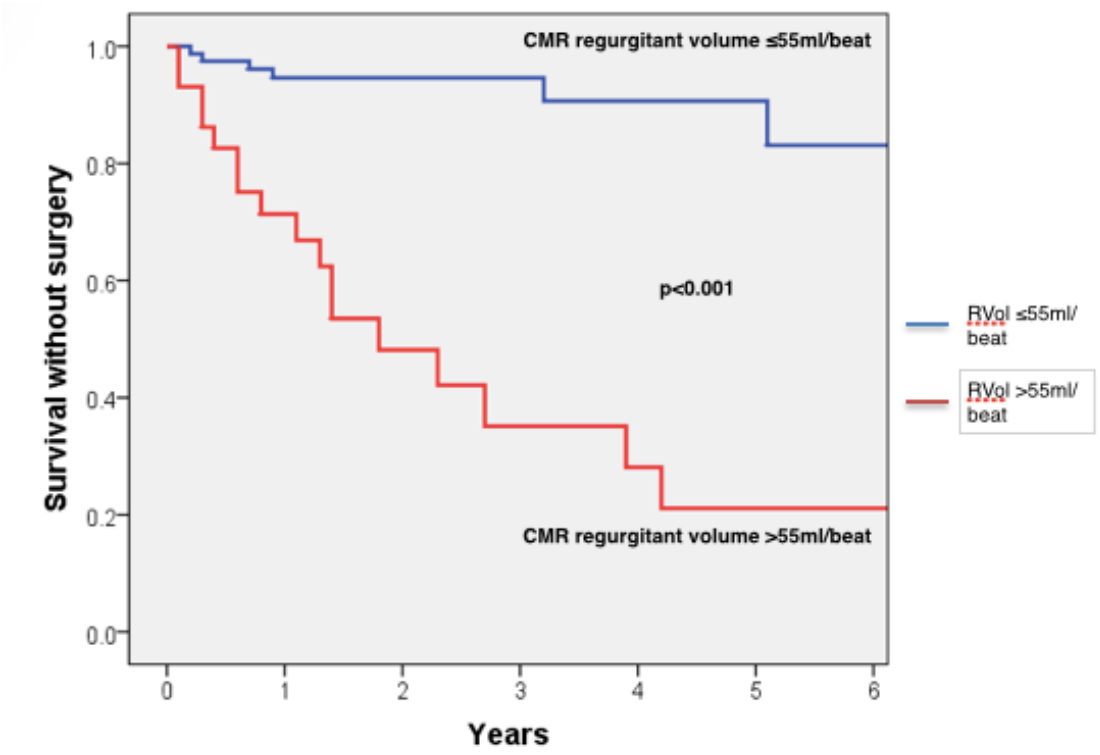

Figure 5.3 Kaplan-Meier graphs for survival without surgery stratified by RVol ≤55ml/beat and >55ml/beat

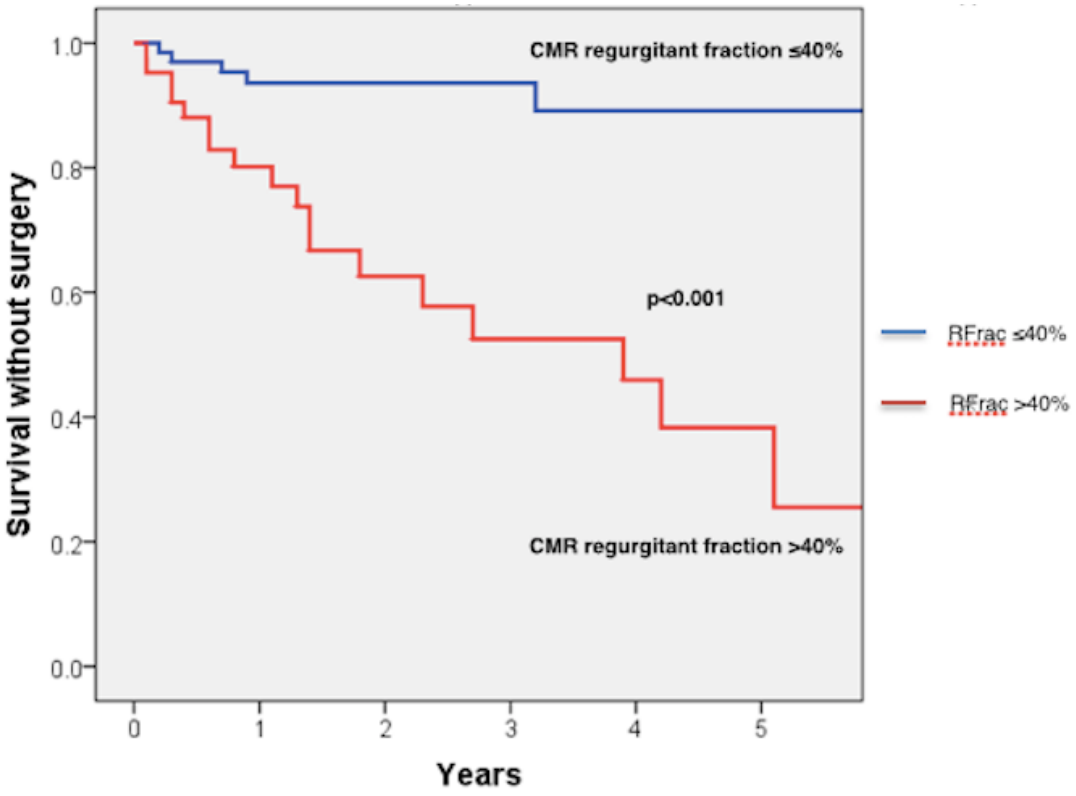

Figure 5.4 Kaplan-Meier graph for survival without surgery stratified by RFrac ≤40% and >40%

5.9 CMR and 2D TTE comparison

5.9.1 Study population

Thirty-nine patients, who were recruited for the main study, also underwent transthoracic echocardiography, as described in section 3.3 above. Of these patients, 2 were unable to complete the CMR scan, and 1 patient had inadequate echo windows to allow quantitative assessment of MR severity. Thirty-six patients had complete TTE and CMR data; the demographics of these patients are shown in table 5.3.

Table 5.3 Demographic data

Patient characteristics (N=36)	
Age, mean (range)	66.9 (35-86)
Male, n (%)	30 (83.3)
BSA, m^2	1.92±.19
Symptom status	
NYHA Class I, n (%)	33 (91.7)
NYHA Class II, n (%)	3 (8.3)
NYHA Class III/IV, n (%)	0 (0.0)
Haemodynamics	
Heart rate, bpm	70±12
Atrial fibrillation, n (%)	10 (27.8)
Systolic BP, mmHg	142±21
Diastolic BP, mmHg	77±11

Values are expressed as mean±SD, unless otherwise indicated; BSA: body surface area; NYHA: New York Heart Association; BP: blood pressure

5.9.2 Echocardiographic and CMR data

Echocardiographic and CMR measures of regurgitant volume were available for all thirty-six patients. Results are displayed in table 5.4.

Table 5.4 CMR and echocardiographic data

CMR data	
LVEDV, ml	190±51
LVESV, ml	61±25
Regurgitant Volume, ml	44±22
Regurgitant Fraction, %	33±13
MR severity by Rvol on CMR	
Mild, n (%)	12 (33.3)
Moderate, n (%)	15 (41.7)
Severe, n (%)	9 (25.0)
Echo data	
MR Vmax, cm/s	486±81
PISA radius, cm	1.03±0.54
Regurgitant Volume, ml	83±86
EROA, cm^2	0.68±0.92
MR severity by Rvol on 2DTTE	
Mild, n (%)	6 (16.7)
Moderate, n (%)	15 (41.7)
Severe, n (%)	15 (41.7)

Values are expressed as mean±SD in the units stated; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; Rvol: Regurgitant volume; MR V max: maximum velocity of the MR jet on Continuous Wave Doppler; PISA: Proximal isovelocity surface area; EROA: Effective regurgitant orifice area.

MR severity was classified by regurgitant volume as mild, moderate or severe, according to the established echocardiographic values(33). According to Rvol measured on CMR, 12 patients (33.3%) had mild MR, 15 patients (41.7%) had moderate MR, and 9 patients (25.0%) had severe MR. In comparison, based on Rvol by 2DTTE, 6 patients (16.7%) had mild MR, 15 patients (41.7%) had moderate MR,

and 15 patients (41.7%) had severe MR. 2DTTE overestimated the severity of MR in 14 patients (38.9%), and underestimated the severity of MR in 2 patients (5.6%).

Figure 5.5 shows the number of patients classified in the same versus different mitral regurgitation severity grade.

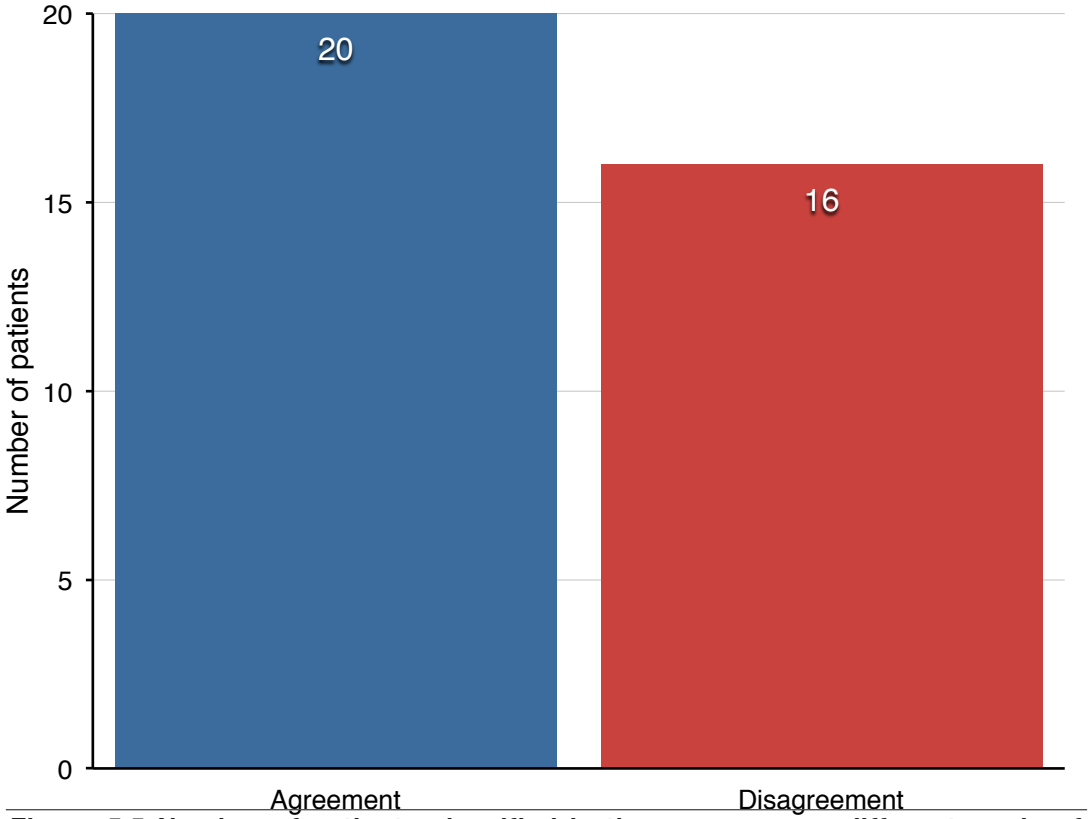

Figure 5.5 Number of patients classified in the same versus different grade of severity of mitral regurgitation, as measured by 2DTTE and CMR

Bland-Altman plots were used to demonstrate the agreement between CMR and 2DTTE measures of RVol (figure 5.6). Two-dimensional transthoracic echo overestimated the regurgitant volume by an average of 36ml/beat (95% limits of agreement -92ml/beat; 164ml/beat). There were two outliers in the dataset, which skewed the data. When these outliers were excluded, 2DTTE overestimated the

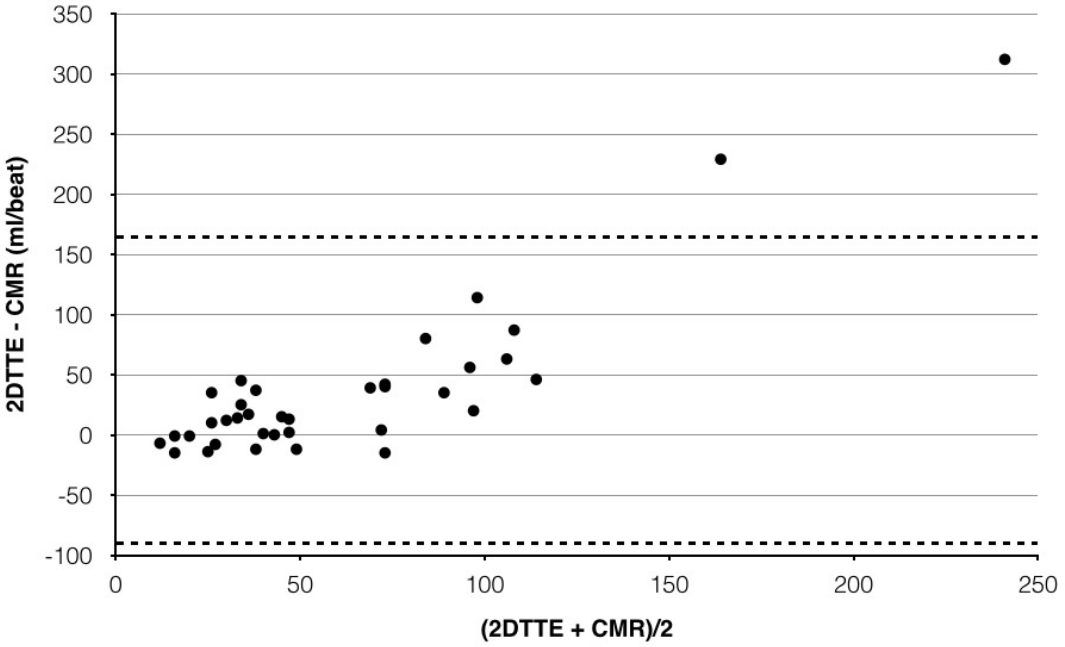

Figure 5.6 Bland-Altman plot demonstrating the agreement in measurements of regurgitant volume between 2DTTE and CMR.

regurgitant volume, compared with CMR, by 22ml (95% limits of agreement -39ml/beat; 83ml/beat).

5.10 Discussion

5.10.1 CMR quantitation of MR is feasible.

This study confirms that the use of CMR in the assessment of MR is feasible. In the four high-volume CMR centres participating in the main study, quantitative measures of mitral regurgitant volume and fraction could be obtained using CMR scanners in routine clinical use, utilising imaging sequences in standard clinical practice. CMR imaging has been well validated for ventricular volumes and for trans-aortic flow by phase-contrast velocity mapping(192-195, 266-269). CMR has now been used in a range of studies of valvular heart disease, including those of patients with MR. The techniques are now established and validated, as described clearly by Cawley et al(272). These studies include only small numbers of participants, and so the study

presented here confirms the feasibility of using CMR in a broader, more real-world population. In the sub-study, the CMR scan was well-tolerated, with 95% of participants completing the scan protocol, although data on tolerability of CMR from other centres was not available.

5.10.2 Quantitative CMR measures of MR for predicting outcome

These data suggest that the quantitative assessment of MR by CMR has the potential to risk stratify patients with primary mitral regurgitation, and allow identification of those at highest and lowest risk of progressing to symptoms or surgery. This is in keeping with previous work in patients with aortic regurgitation(203). This is important as the management of patients with severe MR is contentious and challenging, and markers of risk are poorly defined.

Enriquez-Sarano et al demonstrated that echocardiographic quantitation of MR can be of value in predicting outcomes(12), but echo quantification can be inhibited by poor acoustic windows, geometric assumptions, and eccentric regurgitant jets(274, 275). These factors are less of a challenge in CMR, which has been shown to correlate well with echo and angiographic assessment, with good reproducibility(202, 276, 277). Despite this, there are no published studies of the prognostic significance of CMR quantitation of MR.

The identification of those with regurgitant volumes or fractions above the threshold values described above may select individuals most likely to benefit from the closest follow up. It may also assist in targeting suitable candidates for early surgery for MR. At the other end of the spectrum, those with the lowest regurgitant volumes - the "milder moderate" patients - may be suitable for longer intervals between follow up, which would be both time- and cost-saving. These considerations would need evidence from further studies if they were to be incorporated into standard clinical practice, especially with respect to surgical indications.

The threshold values suggested by the data presented here are similar to those recommended as cut-off values for the echocardiographic assessment of MR(33). These suggest that RVol ≥60ml/beat represents severe MR, which is comparable to the >55ml/beat suggested on ROC analysis of these CMR data. Regurgitant fraction by echocardiography has a slightly higher cut-off value for echo, compared with the proposed value according to the CMR data (≥50% vs >40%, respectively). In those graded as moderate MR on echo criteria, 45% of patients went on to require surgery in the Enriquez-Sarano study, and therefore using the CMR values suggested may be more discriminatory.

5.10.3 Comparison of 2DTTE and CMR for assessment of MR

The PISA method for echo quantification of mitral regurgitation has been validated in experimental and in clinical settings(181-183), but it relies on certain assumptions. Although in a single-centre study reproducibility has been shown to be good(172), inter-observer variability is significant between centres(174). The calculation of PISA = $2\Pi r^2$ assumes a hemispheric isovelocity surface area, and with a non-elliptical regurgitant orifice. If the MR jet interacts with one of the mitral valve leaflets or the wall of the left ventricle, then the PISA is non-hemispheric. Although this can be corrected for using a correcting factor(278), this is assessed by the operator, introducing a significant potential source of error. In eccentric jets, alignment with the Doppler beam is affected, and this leads to further inaccuracies in the calculation of RVol. Where more than one jet of MR is present, the calculation of RVol or EROA using PISA is also inaccurate. Although individual values could be calculated from each PISA and the results summed, this would be very time-consuming. Overlapping PISA jets, or distortion of shells will also create inaccuracies in this setting. CMR measurement of flow and calculation of RVol in MR avoids these assumptions.

The data from 36 patients in the study described above demonstrate a poor correlation between RVol on CMR scanning, and RVol calculated using 2DTTE and the PISA method. 2DTTE overestimated the RVol, when compared with CMR, by a mean of 38ml/beat. Both techniques have been validated using experimental and

clinical methods(33, 202, 272, 279). In a study by Cawley et al, CMR had lower inter- and intra-observer variability when compared to 2DTTE for the measurement of regurgitant volume in AR(196). In the same study, there was significant variability in measures of regurgitant volume for the assessment of MR for both imaging techniques. However, there is no gold-standard method against which CMR and 2DTTE can be measured in order to determine which of these methods is the more accurate.

There are few other studies which compare the two methods of assessing MR. Shanks et al compared CMR assessment of MR with quantitative measures on trans-oesophageal echo, and demonstrated a consistent underestimation of RVol by echo(280), which is the opposite of the finding of this study. Cawley et al assessed both aortic and mitral regurgitation assessment by TTE and CMR(196). Although the main aim of the study was to examine intra- and inter observer measurement variability, the authors also conducted a comparison of inter modality measures of regurgitant severity. This demonstrated a good correlation overall, but with significant scatter of the data. TTE again tended to underestimate the RVol compared with CMR, in contrast with the data reported here. It is not clear why the data from the comparison study reported here differ from both of these studies. Apart from the use of TOE in one study, the only obvious difference in the study populations in that atrial fibrillation was not an exclusion criterion for this study, whereas patients in the other two reported studies were in sinus rhythm. Although this might have made a modest difference, it is unlikely to fully account for the results obtained.

5.11 Conclusions

Quantitative CMR assessment of mitral regurgitation has the potential to be a useful tool for the risk stratification of this patient group, and can assist in predicting outcomes. In trying to identify patients suitable for early surgical intervention with mitral valve repair, these parameters may be useful, but larger clinical trials would be required to confirm this.

Phase-contrast velocity mapping by CMR to measure mitral regurgitant volume does not correlate well with RVol calculated by the PISA method on 2DTTE in a small, unselected population with clinically significant mitral regurgitation.

5.12 Limitations

Although data were gathered in four high-volume CMR centres, the sample size is modest, which limits the strength of the conclusions that can be drawn from these data, as a relatively small number of events occurred. However, the length of clinical follow-up was reasonable (mean 2.3 years, up to 8.6 years).

Although in one centre clinicians were blinded to the results of the CMR scans when deciding on clinical management, scan results were available to the treating physician in the other three centres. This may have resulted in a degree of bias.

Another potential source of bias is that those patients referred by their treating physician for CMR assessment of MR may have been managed more proactively. However there are currently no CMR criteria for recommending surgery in MR, and those patients who went on to have surgery within thirty days of their CMR scan were excluded from the analysis. Patients who underwent surgery for indications outside the established criteria for MR surgery were also excluded. When the progression to surgery of those patients who were prospectively enrolled in a research study was compared to those scanned for clinical purposes, there was no significant differences found between centres (p=0.80 by logrank test).

CMR scanners, and analysis software, were not identical in all of the four different centres, although it would be expected that this would not result in significantly different measures of identical parameters.

When only quantitative echocardiographic thresholds of severity (EROA of < or $\geq$0.40cm^2 are used to predict progression to symptoms or surgery, the separation of survival curves was modest, and the difference in outcome was not statistically significant (p=0.36). Outcomes were similar when regurgitant volume by echo was

assessed, using a threshold of >60ml. However, the numbers in this sub-group were small (n=53), limiting the studies ability to demonstrate an incremental benefit in prognostication for CMR when compared to echocardiography. When CMR quantification uses echocardiographic parameters for MR severity to look at outcomes, separation of the survival curves has been shown to be similar between moderate and severe MR compared with milder regurgitation(281). Larger studies are warranted to assess the utility of CMR and echocardiography in this context, and investigate whether the higher costs and time burden of CMR is justified by a greater ability to prognosticate over echo in these patients.

The sample size for the comparison of 2DTTE and CMR measurements of RVol was small, although it is the same size as that used by Shanks et al, and larger than that reported by Cawley et al. Regurgitant jets in this unselected group were frequently eccentric, and therefore highly likely to be prone to error in the calculation of RVol using the PISA method. However, this is a real-world study and serves to highlight the very real limitations of a widely used method of assessing MR severity.

Chapter 6: Summary

6.1 Summary

6.1.1 Aims of the original work

This work was undertaken with two broad main aims:

- To describe the epidemiology of contemporary VHD in a developed country, through the use of a community-based echocardiographic screening programme, as well as evaluating the related anxiety and acceptability of such a programme;

- To evaluate the use of CMR quantitation for the prognostication in patients with mitral regurgitation, and compare it with a commonly used echocardiographic measure of regurgitation.

In this chapter, the extent to which these aims have been achieved, the utility of these findings in clinical practice, and areas for future research will be discussed.

6.1.2 The epidemiology of valvular heart disease

As discussed earlier in this work, the nature of valvular heart disease in the developed world has changed over the last century. There are few data available on the epidemiology of modern VHD(5, 8), and to date there are no prospective community-based studies of this. The work of OxVALVE PCS delineates the modern prevalence of VHD, and evaluates the relationship of VHD with established risk factors for cardiovascular disease.

The data from OxVALVE PCS presented herein demonstrate that there is a high prevalence of undiagnosed VHD among those aged 65 years and above, and that the prevalence increase markedly with age. Although most undiagnosed VHD is mild in severity, a significant number of this section of the population have more severe VHD, which may need intervention at some stage. In order to benefit from an improved appreciation of the burden of undiagnosed VHD in our population,

clinicians must consider what steps are necessary to decrease the numbers of undiagnosed patients. Education of primary care providers may increase their index of suspicion of VHD in older patients who have some of the risk factors identified by OxVALVE PCS and other studies. An increased awareness of the general population about the importance of VHD and its outcomes may prove beneficial by prompting patients to ask to have their heart listened to when seen by their general practitioner. Engagement with charities and patient awareness groups will also bear fruit. Heart Valve Voice has started work in this area. The charity has run screening days at large sporting events, such as football and cricket matches, to raise awareness and increase detection rates. Whilst enthusiasm for improving detection rates and hopefully outcomes is laudable, careful planning is required to ensure appropriate mechanisms for providing reassurance and follow up to screen positive patients. Opportunistic auscultation may increase the detection rates in primary and secondary care, but will require adequate provision of echocardiographic services in order to assess those found to have a murmur.

Hypertension and atrial fibrillation (AF) were identified as risk factors for undiagnosed valve disease in OxVALVE PCS. The current National Institute for Health and Care Excellence (NICE) guidelines recommend echocardiography in the assessment of many patients with AF(282), and suggest consideration of echocardiography in those with hypertension to look for evidence of end organ damage in certain patient groups(283). Adherence to these guidelines may lead to an increase in the detection rate of VHD.

Increasing age was the strongest predictor of VHD, as might be expected. Understanding of the age patterns associated with VHD allows the targeting of potential screening programmes to optimise uptake and yield. A recent article produced by the British Heart Valve Society suggested screening those aged 75 years and older(43). According to the data from OxVALVE PCS presented here, this approach would mean that over one third (34.1%) of moderate or more valve disease in those aged 65 years or older would go undetected. Arguably these younger patients have the most to gain in terms of life expectancy if their VHD is detected in a timely manner. The finding that a proportion of those who declined the invitation to

participate in OxVALVE PCS did so as they felt they were too old is challenging. Those in the highest age groups have the highest risk of significant VHD, but also have the highest level of comorbidity. Age was also the most frequently cited reason for medical management of VHD in the Euro Heart Survey(5). However, outcomes in the oldest age groups undergoing intervention are also improving with time(37). Patients and clinicians must be made aware of these good outcomes, the potential benefits to patients, the outcomes associated with lack of intervention, and the potential for newer minimally invasive techniques.

As well as elucidating the contemporary prevalence of VHD, the data in chapter 4 also demonstrate the acceptability of a community-based echocardiographic screening programme to the target population. A high level of acceptability is a pre-requisite of a successful screening programme, in terms of yield and also cost-effectiveness. Our study also confirms the feasibility of a community-based programme, when established with the engagement of primary care practitioners. An uptake rate of approximately fifty per cent is lower than other screening studies(205), but formal screening studies would not be subject to the same constraints imposed on OxVALVE PCS by the ethics committee. Increased awareness and promotion of a formal screening programme may lead to a greater proportion of the target population attending for screening. In order for such a programme to be successful, it would need to involve a clearly defined pathway for referral in those found to have VHD, and adequate resources to provide surveillance must also be available. A variety of possible methods for providing such a screening programme have been suggested(43), and the best approach will vary according to the setting.

The potential for provoking high levels of anxiety with screening is an important consideration. The work presented here suggest that, in line with similar studies(166, 167, 169, 255, 259), this is not a significant factor in VHD screening. This provides reassurance, to both clinicians and patients, that an increased detection rate of VHD is not accompanied by an unacceptable burden of anxiety and emotional distress. A proactive approach to minimising anxiety associated with undergoing screening can be attenuated by providing clear descriptions of what patients can expect when attending. Following a positive diagnosis of VHD, patients should be given prompt

reassurance that follow up will be arranged, and adequate and appropriate information on the implications of their diagnosis.

6.1.3 Quantification and prognostication in mitral regurgitation

In chapter 5, it was shown that CMR quantification of mitral regurgitation is associated with outcomes. Those with a regurgitant volume greater than 55ml/beat, or with a regurgitant fraction in excess of 40%, are at high risk of progressing to surgical thresholds. This ability to prognosticate may aid decision making for clinicians, when mitral valve surgery may be considered in asymptomatic individuals with favourable valve morphology. If CMR is to be used for such purposes though, future work should include large clinical trials to assess the potential clinical benefits.

In addition to identifying those patients at higher risk of progression to indications for intervention, lower levels of MR on CMR quantification had a very low chance of progressing within the following few years. The use of these data to rationalise follow up and increase efficiency of surveillance may provide significant cost savings. Larger studies of patients in this category should be encouraged, in order to confirm whether this would be a truly safe approach. The cohort of patients with milder degrees of AR in the OxVALVE PCS may provide a useful starting point for recruitment, as the majority of the patients have already consented to being contacted about relevant future research studies.

The use of the PISA method for calculating regurgitant volume in MR was compared with values derived from CMR imaging in a small sample of patients in the work presented here. Although these data suggest a poor correlation, and highlight the pitfalls of PISA assessment, this is most likely to reflect the small sample size and variety of aetiologies of MR. Non-eccentric jets were common, and these are well recognised to be sub-optimal for PISA measurement. The utility of PISA in appropriate patients should not be discarded. However, PISA is recommended for quantification of MR in international guidelines(33), and these results would suggest

that consideration be given to incorporating CMR assessment in to these guidelines, particularly when echocardiographic assessment may be suboptimal. Further studies should be aimed at larger sample sizes, and also include comparison of newer CMR techniques for measuring flow in mitral regurgitation(284, 285)

6.2 Future areas of study

The potential areas of future study in VHD are multiple, and span all valve lesions, are relevant to a broad cross-section of the population, and involve imaging techniques of all modalities, comparisons of timing and type of intervention, potential serum biomarkers, and risk factors to aid detection of undiagnosed VHD. Some of areas of work were alluded to in chapter 1, and in the discussion sections of the relevant chapters; others are discussed below.

6.2.1 The OxVALVE Population Cohort Study

The cohort of patients recruited to the OxVALVE PCS provides a potentially rich target for future research. The database of echocardiographic and epidemiological data can be exploited as it provides a well-characterised population, and blood and DNA have also been stored on the majority. The majority of participants have also consented to being approached about relevant future studies at enrolment.

The characteristics of participants with aortic sclerosis within the OxVALVE PCS have been interrogated, and linked to imaging studies using CMR. In a separate research project, QRISK2 scores in those with and without aortic sclerosis were compared. This demonstrated that those with sclerosis had a significantly higher QRISK2 score, suggesting that the patients with aortic sclerosis were at a higher cardiovascular risk than those without (unpublished data, personal communication). This is in keeping with previously published data(48, 286).

The blood sampling undertaken as part of the OxVALVE PCS may also provide the opportunity for important future work. There has been significant interest in the utility of serum biomarkers for the prognostication in VHD, particularly the

natriuretic peptides(44, 287-289). The potential for natriuretic peptides, in particular B-type natriuretic peptide (BNP), to be used as a prognostic marker in VHD and to suggest a decline in LV function in these patients has also been demonstrated(44, 45, 290-293). The OxVALVE PCS offers the potential to combine echocardiographic data on valve disease across the spectrum of lesions and severity, with BNP measurements obtained at the point of diagnosis, and potentially prospectively. If progression of VHD could be tracked with a serum biomarker, the potential to identify cut-off levels associated with thresholds for intervention would be greatly increased. DNA has been stored on OxVALVE PCS participants, and genetic studies of those with VHD may help to increase our understanding of the pathogenesis of VHD. An increased understanding at the genetic level may also illuminate new targets for potential intervention, in the same way that understanding of the changes at the histological level have already triggered research(247).

Data from the OxVALVE cohort have already contributed to the EchoNoRMAL Study(294), demonstrating the potential for further collaborative work in VHD in a wide range of future research. The possibility for OxVALVE PCS participants to be approached about participating in studies of imaging techniques; medical, surgical or percutaneous interventions; as well as genetic studies makes this well-characterised cohort a valuable research asset in the study of VHD.

6.2.2 CMR assessment of VHD

The work presented in chapter 5 highlight the potential for CMR quantitation of MR to aid prognostication; this work has now been published(281). There is a real clinical question to be answered when looking at the timing of intervention in MR. Early intervention for severe asymptomatic MR has been advocated by some(295, 296), as prognosis may already be reduced by the time that symptoms or adverse cardiac features have developed. According to the current guidelines, when severe regurgitation is present, the chance of mitral valve repair is considered to be >95%, and surgery is performed in a suitably experienced centre with low mortality rates, there is a class 2a indication for early surgical intervention(230). The balance of surgical risks against poorer outcomes with delayed intervention is a source of

significant debate between proponents of a watchful waiting strategy(297), and those who would advocate early intervention(298, 299). New methods of risk stratification in these patients would therefore be welcomed. Echocardiographic quantitation has been demonstrated to be associated with clinical outcomes in medically managed patients with MR(12), but this study did not aim to identify patients for surgery. The CMR data presented here were targeted at progression to surgery, but larger randomised studies would be needed to confirm these findings, and potentially to assess clinical benefit of using CMR quantitation for early surgery. Similar outcome data using CMR quantification on AR have also been published[203], and these findings would also benefit from larger studies to confirm their utility in clinical practice.

Further examples of novel CMR techniques for quantitation in VHD and potential markers of clinical outcome also bear consideration. In order to improve CMR quantification in the presence of turbulent jets, especially those with high velocities, O'Brien et al have used a novel CMR sequence which utilises ultrashort echo times(284). The use of this new sequence was associated with lower levels of flow error when compared to conventional flow sequences. Mirroring the work done on the assessment of left ventricular fibrosis in AS using CMR methods(300), Edwards et al looked at the quantification of LV fibrosis in chronic degenerative MR. In a small study of 35 patients with MR, they found fibrosis in MR to be associated with reduced myocardial deformation and exercise capacity(301).

6.3 Conclusion

In conclusion the work presented in this thesis demonstrates the contemporary epidemiology of VHD, and refutes the suggestion that attempts to increase detection rates may result in unacceptable levels of anxiety. The use of CMR quantification in MR can be used to refine prediction of outcome, and PISA quantification in this group does correlate well with CMR measures of regurgitant volume.

Healthcare planning and resource allocation for cardiovascular disease should take account of these findings. Adequate investment in provision of care for these patients is essential in order to avoid a high burden of heart failure related costs, and a

degradation in the quality and quantity of life of those with this condition. Investment should be targeted on improved methods of assessment and prognostication, as well as on increased detection and evidence-based intervention. The use of the programmes such as OxVALVE PCS, and focus on newer imaging parameters such as those discussed here, need to be linked to outcome studies to establish their roles in the optimal pathway of care for those with valvular heart disease.

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Appendix 1

B2

ID ☐☐☐

OXVALVE

Questionnaire

REC Study number: 09/H0502/58

The Heart Screening Programme has only recently been set up in Oxfordshire.

We are interested in your views about the programme so we can improve it for the future.

There are no right or wrong answers, as we are interested in your personal views and feelings

If you have any questions about this questionnaire, please contact:

Study Co-ordinator
DVD Group Co-ordinating Centre
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Version 1.2 19 June 2009

We would like to know how you feel at the moment

A number of statements which people have used to describe themselves are given below.

Impressions on Screening

We are interested in your initial impressions of the screening programme. Please circle the number most appropriate to your answer for the questions below.

1. Were you aware of this screening programme *before* you received your invitation?

Not aware	Unsure	Aware
1	2	3

2. Did you find receiving your invitation by post satisfactory?

Definitely not	No	Unsure	Yes	Definitely yes
1	2	3	4	5

3. Would you have preferred receiving an invitation for screening in person while visiting the surgery for another reason?

Definitely not	No	Unsure	Yes	Definitely yes
1	2	3	4	5

4. How important do you think it is for you to have health screening in general?

Not important	Slightly important	Unsure	Important	Very important
1	2	3	4	5

5. How important do you think it is to have tests to check your heart valves are healthy?

Not important	Slightly important	Unsure	Important	Very important
1	2	3	4	5

6. Do you think the initial invitation letter you received explained the tests clearly?

Definitely not	No	Unsure	Yes	Definitely Yes
1	2	3	4	5

7. Would you have this test to check your heart valves again?

Definitely not	No	Unsure	Yes	Definitely yes
1	2	3	4	5

Further comments:

Please write any comments or concerns you have below.

Thank you for taking the time to complete this questionnaire

Please return this to the surgery receptionist in the envelope provided.

Appendix 2: Papers

Valvular heart disease

openheart

The OxVALVE population cohort study (OxVALVE-PCS)—population screening for undiagnosed valvular heart disease in the elderly: study design and objectives

Sean Coffey,[1] Joanna L d'Arcy,[1] Margaret A Loudon,[1] David Mant,[2] Andrew J Farmer,[2] Bernard D Prendergast,[1] for the OxVALVE-PCS group

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ABSTRACT

Introduction: Valvular heart disease (VHD) is an increasingly important cardiac condition, driven by an ageing population and lack of progress in the development of medical therapies. There is a dearth of accurate information to guide decision-makers in the development of strategies to combat VHD, and no population-based study has been performed specifically to investigate its contemporary epidemiology. This document describes the design and methodology of the OxVALVE population cohort study (OxVALVE-PCS), which was conceived to address this need.

Methods and analysis: Participants aged 65 years and older attending a participating general practice in Oxfordshire, UK, are invited to attend a screening examination. Exclusion criteria include previously diagnosed VHD, inability to provide consent, terminal illness or excessive frailty. Demographics, a focused cardiovascular history and vital signs are recorded at the initial screening examination, accompanied by an echocardiogram. Any finding of significant VHD triggers a separate, more formal echocardiographic assessment (including acquisition of a three-dimensional dataset) and collection of blood samples for future genetic and biomarker analysis. Participants provide consent for longitudinal follow-up and enrolment in future cohort substudies. We also assess the acceptability of community-based echocardiographic examination and compare self-assessed quality of life between those with and without VHD.

Conclusions: OxVALVE-PCS will provide contemporary epidemiological data concerning the community prevalence of undiagnosed VHD, facilitate accurate deployment of scarce resources to meet the anticipated increase in demand for VHD-associated healthcare and create a series of subcohorts with carefully defined genotypes and echocardiographic phenotypes for long overdue clinical studies.

Ethics and dissemination: This study was approved by the local research ethics committee (Southampton, UK; REC Ref: 09/H0502/58).

Results: Results will be submitted for publication in peer-reviewed scientific journals.

KEY MESSAGES

- Valvular heart disease is becoming an increasingly important problem due to the aging of the population.
- Accurate information on the epidemiology and the natural history of the different forms of valve disease in the modern era is limited.
- The OxVALVE population cohort study aims to investigate the contemporary epidemiology of previously undiagnosed valvular heart disease in the elderly.

INTRODUCTION

Valvular heart disease (VHD) is a significant cause of morbidity and mortality in the general population.[1] There are few randomised controlled trials of medical therapy, all with negative results,[2–4] and international guidelines are largely based on expert consensus.[5] VHD is poorly researched at basic scientific and clinical level in comparison to other areas of cardiovascular disease. Principal limitations are the diverse nature of patients with VHD, inability to identify individuals at the earliest stages of disease and lack of an appropriate investigational infrastructure. VHD is frequently asymptomatic and can present late, and often requires significant interventions (surgical or percutaneous) after symptomatic presentation. Early detection and intervention may improve outcome and it is anticipated that detection could be undertaken in some primary care settings.

Previous population-based studies examining the prevalence of VHD have a number of limitations. Most were conducted via retrospective review of echocardiographic data collected initially to characterise ventricular structure and function,[6–9] while one which prospectively recorded valvular disease was primarily focused on calculations of left

ventricular mass.[10] Furthermore, all of these studies were initiated in the previous millennium—as the population ages rapidly, there is a pressing need for contemporary epidemiological data.

We designed the OxVALVE population cohort study (OxVALVE-PCS) to specifically examine the prevalence of VHD in a contemporary cohort of elderly men and women living in Oxfordshire, UK. Collection of a well-characterised and annotated database of a large number of cases of VHD, including the full variety of types and severity, will also allow the identification of specific suitable populations for future clinical research studies. Such studies may not be confined to pharmacological interventions, but may include surgical and percutaneous procedures, novel imaging techniques and devices, genetic associations or new paradigms of clinical management, including evaluation of the impact of community screening and integration within primary and secondary healthcare service provision. Lay participants have contributed to the design and implementation of the programme. In this article, we focus on the design of the initial cross-sectional study and include details of follow-up where appropriate.

STUDY OBJECTIVES

Primary

To establish a longitudinal cohort of patients with previously undiagnosed VHD via an echocardiographic screening programme.

Secondary

1. To define the prevalence of VHD in the Oxfordshire population.
2. To assess the influence of covariates, such as prior cardiovascular events, family history, obstetric history, body mass index (BMI) and medications on the likelihood of VHD.
3. To assess and compare morbidity and mortality in participants with and without VHD.
4. To explore the association between VHD and socioeconomic status.
5. To assess the acceptability of echocardiographic screening for VHD and to identify the extent and predictors of anxiety experienced.
6. To establish well-annotated phenotypes with linked and stored blood samples in the study population for future research.
7. To establish the prevalence of other cardiovascular disorders (in particular hypertension and left ventricular dysfunction) in participants not known to have VHD.

METHODS AND ANALYSIS

The OxVALVE protocol was developed according to STROBE guidelines for the conduct and reporting of observational studies.[11]

Study design and overview

OxVALVE-PCS is a prospective cohort study examining the prevalence, incidence and outcomes of participants aged 65 and older with newly diagnosed VHD. Participants attend an initial visit at their local general practice, followed by a second visit at their local hospital if VHD is detected (figure 1).

Setting

We invited a number of general practices within Oxfordshire to participate in the study. Recruitment began in 2009 and is expected to continue until 2015. The first study visit with screening echocardiography is held in the general practice, and those with newly diagnosed VHD are invited to a second visit at Oxford University Hospitals Trust (a secondary and tertiary referral network of hospitals serving Oxfordshire). Clinical data are collated at visit 1 using OpenClinica open source software V.3.0.4.1 (OpenClinica LLC, Waltham, Massachusetts, USA).

Participants

The entire population of each participating practice is screened and all those aged 65 years or greater without known VHD are invited to participate. Exclusion criteria are a previous diagnosis of VHD (identified using relevant diagnostic codes), terminal illness, immobility or general frailty (as judged by the general practitioners (GPs)), or inability or unwillingness to provide informed consent. Potential study participants are identified from practice lists by the practices themselves—all patient identifiable information is held by the GPs until participants consent to take part in the study. The Oxfordshire population aged 65 years and over consisted of 103 742 adults in the 2011 census (45% men), with ethnicity as follows: Caucasian 97.8%, Asian 1.1%, African-American 0.6%, mixed ethnicity 0.3%, other ethnicity 0.1%.[12] Potential participants are invited by letter with a single follow-up reminder to non-responders. Telephone contact was not permitted by the Research Ethics Committee. Those declining participation are asked to fill in a brief response indicating their reasons to allow detection of study bias.

Study details

Visit 1

Participants attend a dedicated research clinic at their general practice, where they undergo an eligibility check; provide informed consent, baseline demographics and a brief medical history and undergo a limited cardiovascular physical examination followed by transthoracic echocardiography. Participants are asked to self-complete two questionnaires, and provide comments about their participation in the study. When necessary, the National Health Service (NHS) Language Line Interpreting Service is used to ensure that all participant queries relating to the study are answered and that true informed consent is granted.

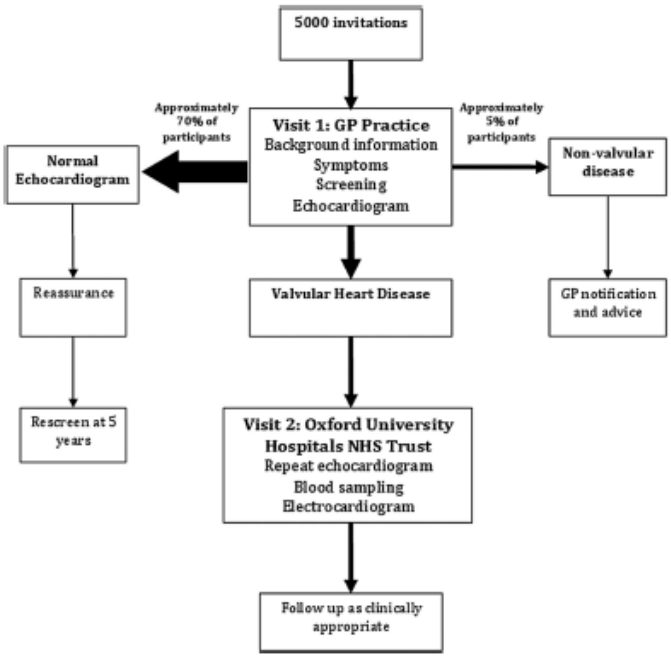

Figure 1 Overview of the OxVALVE population cohort study (GP, general practitioner; NHS, National Health Service).

Classification

Participants are classified according to whether they have a normal echocardiogram, newly diagnosed VHD or an alternative cardiac pathology (figure 1). Each participant, along with his or her GP, is sent a letter summarising the findings and any further action plan. The threshold for inclusion in the screen-positive group is intentionally low to allow all manifestations of VHD to be captured with careful prospective follow-up. Participants in this group are invited to attend a specific OxVALVE clinic at a site within the Oxford University Hospitals NHS Trust for more detailed characterisation.

Visit 2

Participants with newly noted VHD undergo an ECG, a more sophisticated echocardiogram and blood sampling. A letter confirming the echocardiographic findings is sent to the participants and their GPs.

Follow-up

Participants with a normal echocardiogram are invited to attend a follow-up visit 5 years after initial evaluation to determine the period incidence of VHD and assist in the identification of initial 'false-negative' findings. Participants are also tracked via UK national databases (Medical Research Information Service, Hospital Episode Statistics and Myocardial Ischaemia National Audit Project) in order to provide a comparison of morbidity and mortality between screen-positive and screen-negative groups. We recognise that there may be participants with false-negative scans in the screen-negative group—the proposed follow-up programme will assess the clinical importance of an initial negative screening echocardiogram rather than a definitive absence of VHD. Continued follow-up in accordance with current European Society of Cardiology guidelines is offered to those with clinically significant newly diagnosed VHD or alternative cardiovascular pathology.

Variables

The primary measure is the new diagnosis of VHD detected by echocardiography performed in the primary care setting.

Secondary measures are:

1. Impressions of screening (questionnaire assessment)
2. Morbidity and mortality (national database tracking)
3. Health status measurement (EuroQol-5D (EQ-5D))
4. Left ventricular function
5. Two-dimensional (2D) measurements of major cardiac structures (ventricles and atria)
6. ECG abnormalities
7. Biomarker abnormalities

Predictor and confounder variables recorded are demographics, medical and social history, medication, blood pressure, BMI, genetic profile and socioeconomic status.

Data sources/measurement

Clinical assessment

At visit 1, information is obtained concerning age, gender, time spent in countries other than the UK,

ethnicity, cardiovascular medical history, smoking status, medication and the presence or absence of heart failure symptoms (New York Heart Association classification (NYHA) or chest pain (Canadian Cardiovascular Society (CCS) score)).[13] Women are asked the number of pregnancies and details of any associated complications. A focused clinical examination is then performed consisting of height, weight, pulse and blood pressure (Omron M6 blood pressure monitor, Kyoto, Japan) and assessment of the presence or absence of ankle oedema. An echocardiogram is performed and the participants complete two questionnaires.

Echocardiography—visit 1

Echocardiography is performed by the British Society of Echocardiography (BSE) accredited sonographers or physicians using a Vivid-Q portable machine (Vingmed-General Electric, Horton, Norway)—the same pool of operators also perform visit 2 scans. BSE accreditation is directly comparable to European Association of Cardiovascular Imaging accreditation in transthoracic echocardiography (with which there is reciprocal recognition). A two-beat clip for each image is stored in sinus rhythm, while a five-beat clip is acquired in patients with irregular rhythm (usually atrial fibrillation). Measurements are not recorded immediately following an ectopic beat. When assessing regurgitation with colour flow Doppler, the Nyquist limit is set to 50–60 cm/s. For views of each valve, the colour gain is optimised until just before 'speckling' occurs.

In addition to standard acquisition protocols, the following images/measurements are obtained (corresponding views listed in brackets):

- Zoomed images of the aortic valve, aortic root and ascending aorta, along with any regurgitation (parasternal long and short axis).
- Diastolic function assessment (to include mitral valve inflow, pulmonary vein flow and pulsed wave (PW) tissue Doppler imaging (TDI) of the septal and lateral walls).
- Tissue velocity imaging (TVI) 2D loop of left ventricle.
- Continuous wave Doppler through aortic, mitral and tricuspid valves to demonstrate presence/absence of any regurgitation (apical five/four/three and two-chamber views, as appropriate).

Left ventricular ejection fraction is assessed using the Teichholz calculation if left ventricular systolic function is qualitatively normal, accompanied by experienced visual assessment of overall systolic function. In this setting, the Teichholz calculation performs well[14]—a recent study showed closer values than biplane ejection fraction assessed using the gold standard of cardiovascular magnetic resonance.[15] Visual assessment, despite its semiqualitative nature, is also accurate when undertaken by experienced practitioners.[16 17] Abnormal systolic function leads to a formal biplane volumetric assessment of ejection fraction, classified as follows: normal ≥60%, mildly impaired 45–59%, moderately impaired 35–44% and severely impaired <35%. A high threshold for normality was chosen to ensure that a large proportion of participants underwent volumetric assessment.

Diagnosis of VHD

Valve anatomy and physiology are assessed in accordance with BSE criteria for stenosis and regurgitation,[18] which were adapted from internationally recognised guidelines.[19 20] Aortic valve sclerosis is defined by the presence of all of the following echocardiographic features:

- Focal areas of thickening and increased cusp echogenicity (calcification)—minor leaflet tip thickening in itself is insufficient and abnormal cusp echogenicity must be demonstrated.
- Normal or near normal cusp mobility.
- Maximum aortic valve transvalvular velocity less than or equal to 2.5 m/s.

These criteria are minor modifications of the European Association of Echocardiography/American Society for Echocardiography guidelines.[20] A calcified or thickened aortic valve with transvalvular velocity greater than 2.5 m/s is diagnosed as aortic stenosis.

Extrapolating from the American Society of Echocardiography guidelines,[19] we define mild (as opposed to trivial or 'physiological') valvular regurgitation if the regurgitant jet has a clear origin and is visible in more than one view on colour Doppler. Trivial mitral regurgitation requires the presence of normal mitral valve anatomy and a regurgitant jet that extends less than 1 cm into the left atrium at Nyquist limit 50–60 cm/s in all views.

Classification of newly diagnosed VHD

A low threshold for inclusion in the screen-positive group is specified in order to capture all manifestations of VHD and establish cohorts for future study. As a general rule, any left-sided valve disease (except 'physiological' regurgitation) is considered significant while isolated right-sided valve disease is only considered significant if moderate or greater in severity. A patient is referred for visit 2 assessment if any of the following conditions are identified:

- Sclerotic aortic valve
- Mild or above aortic stenosis or regurgitation
- Mild or above mitral stenosis or regurgitation
- Mild or above tricuspid or pulmonary stenosis
- Moderate or above tricuspid or pulmonary regurgitation

Echocardiography—visit 2

An IE33 machine (Phillips, Eindhoven, The Netherlands) is used to obtain echo images at visit 2 by a sonographer blinded to the visit 1 findings. A replica dataset is obtained, with the addition of the following images (corresponding views):

- Zoomed images of mitral valve (parasternal long and short axis)
- TVI at mid-left ventricle (parasternal short axis)

- Optimisation for Simpson's biplane volumetric assessment (apical four-chamber and two-chamber view)
- Biplane left atrial volumes (X-plane through centre of mitral annulus)
- PW TDI of inferoseptal and anterolateral walls (apical four-chamber view)
- Three-dimensional (3D) datasets in those with adequate 2D images

For 3D dataset acquisition, a single cardiac cycle is constructed of four stitched cycles using images acquired with and without breath hold. The 3D datasets (and corresponding views) are as follows:

- Three full volume loops focusing on mitral and aortic valves (parasternal long axis);
- Three full volume loops focused on the left and right ventricle with mitral annulus still visible (apical four-chamber view);
- Three full volume loops of 3D zoom over mitral valve, commissures and annulus (apical four-chamber view).

Image reporting and storage

The echocardiographic study is reported by the performing operator and stored using EchoPac V.110 (Vingmed-General Electric, Horton, Norway) with digital versatile disk backup. Strain analyses (whether 2D or 3D) will report the frame rate used in the final image analysis.

Quality assurance

Rolling review with blinded re-reporting of a random sample of approximately 15% of scans by the pool of BSE accredited sonographers and physicians is undertaken for quality assurance and to ensure consistency of reporting across sites. Reproducibility between the original assessment of VHD and that delivered by the group will be reported using Cohen's κ coefficient. When differences in reporting emerge, scans are reviewed by an independent blinded cardiologist.

Questionnaires

To explore associations between VHD and health status, all participants complete the Spielberger State-Trait Anxiety Index (STAI) and EQ-5D questionnaires during visit 1. In addition, a random sample of participants (approximately 10–20%) receives a postal version of the STAI and EQ-5D questionnaires at the point of study invitation and again 3 months after visit 1. There are natural comparisons to be made between our study, using as it does cardiac imaging in a primary care setting in participants without known heart valve disease, and a screening programme. We therefore assess the acceptability of echocardiographic screening for VHD in primary care using our own 'Impressions of Screening' questionnaire, which is completed during visit 1.

Spielberger State-Trait Anxiety Index

The STAI is a reliable and widely used measure of anxiety. We wished to examine how echocardiography affects our asymptomatic participants, and in particular whether the finding of mild VHD, which is usually clinically silent, causes them anxiety. We use the state scale, which focuses on short term as opposed to general feelings or traits, and the 6-item short form assessment, which has proven reliability and validity but offers a significant reduction in completion time compared with the original 40-item STAI questionnaire.[21]

Impressions of Screening questionnaire

We devised a short questionnaire which all participants complete immediately after their visit 1 echocardiogram to investigate general views concerning VHD screening. This was based on a questionnaire we had previously used to assess acceptability of faecal occult blood testing to detect colorectal carcinoma.[22]

EQ-5D questionnaire

The EQ-5D assesses self-described health status across a number of domains that is then condensed into a single index.[23] It has been widely used and extensively validated across different populations and disease states.[24] We elected to use the EQ-5D without visual analogue scale.

Blood tests and genetic profiling

Visit 2 participants undergo venepuncture and approximately 20 mL blood is divided into separate tubes containing EDTA, heparin and serum-separating tubes (Becton Dickinson, Franklin Lakes, New Jersey, USA). These are refrigerated immediately and centrifuged within 2 h at 1300 rpm for 10 min at 4°C. The plasma/serum fraction is removed and stored in 500 µL aliquots. Whole blood stored on EDTA is refrigerated at 4°C until DNA extraction is performed within 5 days of sample collection. DNA is extracted using the QIAamp DNA blood Midi kit (Qiagen, Venlo, The Netherlands) according to the manufacturer's instructions and, along with the remaining samples, is stored for future analysis at −80° C with Oxford Radcliffe Biobank. Separate EDTA plasma samples are collected for B-type natriuretic peptide (BNP) analysis and these are frozen prior to analysis for up to 3 days following centrifugation and separation. BNP analyses utilise the Siemens ADVIA Centaur analyser (Siemens Healthcare Diagnostics, Frimley, UK) in accordance with manufacturer's recommendations. Sample registration and tracking are collated using Sapphire V.5.1 (LabVantage, Somerset, New Jersey, USA).

Bias

A brief questionnaire identifying reasons for non-participation is sent to those declining the invitation, allowing us to examine potential bias owing to differences between participants and non-participants. Once results are collated, we will report the final study uptake and provide comparisons of those accepting and declining the invitation to participate.

Diagnosis of VHD using echocardiography may also introduce bias since this modality has limitations in image acquisition, particularly in participants with obesity or

significant lung disease. Given the association between these conditions and cardiovascular disease, this may lead to underestimation of the prevalence of VHD.

Study size

We aim to invite 5000 individuals from the Oxfordshire population to participate in OxVALVE-PCS. Based on previous experience in community heart failure screening programmes, it is expected that approximately 4000 (80%) will participate. The threshold for inclusion in the screen-positive group is low to allow all manifestations of VHD to be captured with subsequent careful prospective follow-up. Based on a detection rate of 30%, this total of 4000 participants will identify approximately 1200 cases of newly diagnosed VHD. However, most of the VHD detected will be mild. In the meta-analysis by Nkomo *et al*,[1] moderate-to-severe VHD was detected in 1.3% of those aged 65–74 years. Our sample size of 4000 participants was therefore chosen to detect at least 50–60 participants with moderate-to-severe VHD.

Quantitative variables and statistical methods

We describe methods of statistical analysis for the primary outcome—secondary outcome analyses will be conducted in a similar way. Participants with missing key data (in particular, measurement of ejection fraction, left ventricular, left atrial and interventricular septal dimensions) will be removed from the analysis. Descriptive statistics will be presented using means and SDs for continuous variables and counts (percentages) for categorical variables. t Test and χ^2 test will be used to explore associations between VHD and quantitative and categorical variables, respectively. Trends across age groups will be examined using the Cochran-Armitage test, and logistic regression models will be used to test the association of VHD (as previously defined) with clinical and echocardiographic characteristics. Initial regression models will be unadjusted, and then adjustments made for potential confounders such as age, sex, BMI, study centre, clinical variables and socioeconomic status. All results from the regression analysis will be expressed as ORs with 95% CIs and a two-tailed p value <0.05 considered statistically significant.

Ethics and dissemination

Research sponsorship is provided by the Oxford Radcliffe Hospitals NHS Trust (precursor to Oxford University Hospitals Trust, Research and Development Reference 5942).

The results of the study will be submitted for publication in peer-reviewed scientific journals. We will also provide summaries of findings in a more accessible format through a newsletter to our participants and on our website (http://www.oxvalve.nhs.uk).

DISCUSSION

OxVALVE-PCS is the first population-based prospective cohort study focusing primarily on investigating the epidemiology of VHD in the elderly. The study also assesses the impact of echocardiographic screening for occult VHD and other cardiovascular disease in primary care for the first time, allowing earliest detection of not only VHD but also other key cardiac conditions (eg, latent left ventricular systolic dysfunction). Participants with previously unidentified VHD may benefit from detailed follow-up and participation in future research studies of novel therapies. In anticipation of the increasing prevalence of VHD in the growing elderly population, the study will also direct healthcare policy and financial planning by accurate delineation of the contemporary epidemiology of VHD in a European nation.

Limitations

OxVALVE-PCS will underestimate the overall prevalence of VHD as a result of (1) limited echocardiographic imaging in some participants, (2) exclusion of the very frail elderly and (3) exclusion of those with known VHD.

Assessment of a healthy asymptomatic population sample and exclusion of participants with known VHD will systematically underestimate overall prevalence. The use of echocardiography has risen steadily over the years, with an average of 1.1 echocardiograms performed per person per year in a recent US-based Veterans Health Association study.[25] Participants with comorbidities predisposing to VHD, especially ischaemic heart disease, are likely to have had an echocardiogram based on current recommendations.[26] Any incidental (even mild) VHD would exclude a participant from our study, leaving our sample potentially consisting of participants with a lower range of comorbidity than the general population. For example, pre-existing bicuspid aortic valve disease is likely to present clinically in participants less than 65 years of age—our study design will therefore systematically underestimate its prevalence in the overall population. However, since one of our aims is to determine the prevalence of newly diagnosed VHD, our approach is integral to the study with the large sample size still allowing us to detect a significant number of new cases of VHD. Amalgamation of the prevalence of known and newly diagnosed VHD will be carried out at the time of final data analysis using pre-existing primary and secondary care databases.

The epidemiology of VHD in frail elderly adults was investigated in early echocardiographic studies conducted among participants in long-term residential care.[27–29] Frail elderly participants are often unable or unwilling to tolerate medical or surgical therapies—intervention earlier in the course of the disease, before the onset of frailty is more acceptable and less risky. OxVALVE-PCS was designed pragmatically in conjunction with primary care colleagues and aims to provide epidemiological information on a population where

VHD may be more amenable to intervention in the future. Although exclusion of the very frail elderly reduces the overall number of participants with VHD, the large sample size provides the study power required to accurately delineate different subpopulations of VHD.

We also recognise that our study population may not be representative of other areas of the UK, Europe and beyond. Consistent with local census data, 98% of the population sampled by OxVALVE-PCS is of white ethnicity, compared with, for example, 86% of the elderly US population.[30] Clearly, the prevalence of VHD may vary in areas with greater ethnic mix where previous exposure to such diseases as rheumatic fever may be a major confounding variable. Socioeconomic factors may also bear influence on the prevalence of VHD, and this will be the subject of further investigation. However, the characteristics of the OxVALVE-PCS population are not dissimilar to those of the total population of England and Wales, where 95% of the elderly are of white ethnicity—despite increasing heterogeneity in younger age groups, older age groups in many high-income countries remain largely ethnically homogenous.[12] Our findings are therefore germane to other similar populations.

CONCLUSIONS

OxVALVE-PCS is a large population-based prospective study that will provide important new insight into the epidemiology of VHD. Cardiac services are under pressure to deal cost-effectively with 'the new cardiac epidemic'.[31] The study will therefore be important in providing clinicians and health service planners with the evidence necessary to plan for the future.

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Contributors The original study was designed by JLdA, DM, AJF and BDP. The protocol was written by SC and MAL, with input from the other authors. All authors reviewed and approved the final draft.

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Competing interests None.

Ethics approval The study was granted ethical approval by the local research ethics committee (Southampton, UK; REC Ref: 09/H0502/58).

Provenance and peer review Not commissioned; externally peer reviewed.

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CLINICAL RESEARCH
Valvular heart disease

Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study†

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Background Valvular heart disease (VHD) is expected to become more common as the population ages. However, current estimates of its natural history and prevalence are based on historical studies with potential sources of bias. We conducted a cross-sectional analysis of the clinical and epidemiological characteristics of VHD identified at recruitment of a large cohort of older people.

Methods and results We enrolled 2500 individuals aged ≥65 years from a primary care population and screened for undiagnosed VHD using transthoracic echocardiography. Newly identified (predominantly mild) VHD was detected in 51% of participants. The most common abnormalities were aortic sclerosis (34%), mitral regurgitation (22%), and aortic regurgitation (15%). Aortic stenosis was present in 1.3%. The likelihood of undiagnosed VHD was two-fold higher in the two most deprived socioeconomic quintiles than in the most affluent quintile, and three-fold higher in individuals with atrial fibrillation. Clinically significant (moderate or severe) undiagnosed VHD was identified in 6.4%. In addition, 4.9% of the cohort had pre-existing VHD (a total prevalence of 11.3%). Projecting these findings using population data, we estimate that the prevalence of clinically significant VHD will double before 2050.

Conclusions Previously undetected VHD affects 1 in 2 of the elderly population and is more common in lower socioeconomic classes. These unique data demonstrate the contemporary clinical and epidemiological characteristics of VHD in a large population-based cohort of older people and confirm the scale of the emerging epidemic of VHD, with widespread implications for clinicians and healthcare resources.

Keywords Epidemiology • Valvular heart disease • Echocardiography • Health policy and outcome research

Introduction

Valvular heart disease (VHD) is an important cause of reduced functional capacity, heart failure, arrhythmia, recurrent hospital admission, and early mortality. The combination of an ageing population, earlier diagnosis, and greater availability of surgical and percutaneous interventions heralds a major increase in the healthcare resources required for its optimal management.[1,2]

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There is therefore a pressing need to better understand the contemporary clinical and epidemiological characteristics of VHD, particularly in the elderly population. Previous studies have either been hospital based[3] or retrospective in design[4,5] and thus subject to significant selection biases. Broader epidemiological studies provide limited data and there are no contemporary prospective large-scale population-based studies specific to VHD in developed countries. Available retrospective data demonstrate an increasing prevalence with age, predominantly as a result of degenerative pathophysiology.[3–5] A major increase in the prevalence of VHD would therefore seem an inevitable consequence of the anticipated increase in the number of older people in the population. Reliable contemporary data demonstrating the prevalence of VHD are an essential requirement for researchers and clinicians to improve understanding of its underlying pathophysiology, risk factors, and natural history; and for policy makers and economists to plan the provision of health services for both surgical and percutaneous interventions and long-term medical care.

Accordingly, we established a large prospective study to provide a unique population-based evaluation of the contemporary clinical and epidemiological characteristics of VHD and create well defined and carefully phenotyped cohorts with individual valve lesions for future study. Herein, we present a cross-sectional analysis of the population prevalence of undiagnosed and known VHD in the first 2500 participants and quantify the community prevalence of milder forms of VHD for the first time.

Methods

The OxVALVE Population Cohort Study (OxVALVE-PCS) is an ongoing prospective cohort study conducted in Oxfordshire, UK. Methodological details have been previously reported elsewhere.[6] In brief, subjects aged 65 years and older without known VHD who were registered with one of five primary care medical centres were invited to participate. Younger subjects were excluded since (i) previous retrospective studies have demonstrated that the prevalence of VHD is low in those aged <65 years[4] and (ii) uptake of community screening was likely to be low in those with work or family commitments. The participating medical centres were representative of the local population demographics and selected for the availability of accurate patient databases with comprehensive search facilities. Subjects with a previous diagnosis of VHD (identified using relevant National Health Service diagnostic Read codes) were not included in the echocardiographic study but their diagnostic data were collected to derive total prevalence. Exclusion criteria included terminal illness and immobility or general frailty precluding attendance (as judged by the general practitioner/family physician). Eligible subjects received an initial study invitation letter with a single follow-up reminder to non-responders—further contact with potential study participants was not permitted by the local research ethics committee which approved the study. All participants provided written informed consent.

Participant assessment

An investigating physician or British Society of Echocardiography (BSE) accredited sonographer undertook clinical and transthoracic echocardiographic assessment in the participant's local medical centre. Socioeconomic class (SEC) was determined using Index of Multiple Deprivation (IMD) scores based upon home address postcode. Each SEC corresponds to 20% of the national population (with SEC1/SEC5 denoting the least/most deprived quintiles, respectively).

Diagnostic criteria

The primary outcome was a finding of mild or more severe left-sided VHD or moderate or more severe right-sided VHD. Valve anatomy, physiology, and severity of VHD were defined according to BSE criteria[7] and international guidelines.[8,9] Aortic sclerosis (AoScl) was defined according to 2009 European Association of Echocardiography/American Society for Echocardiography guidelines[9]—thickening and focal calcification of the aortic valve leaflets, with normal or near normal cusp mobility and maximum aortic transvalvular velocity ≤ 2.5 m/s. Aortic stenosis (AS) was defined as aortic valve thickening or calcification with a maximum aortic transvalvular velocity >2.5 m/s.

Statistical analysis

Participants were stratified by age and gender to explore the prevalence of VHD and examine demographic and clinical characteristics. Descriptive statistics for the study cohort are presented using means and standard deviations (SD) for continuous variables, and counts (percentages) for categorical variables. Student's *t*-test and Chi-squared test or Fisher's exact test were used to explore associations between VHD and quantitative and categorical variables, respectively. Logistic regression models were used to assess associations of newly diagnosed VHD. For multivariate regression, all variables with initial univariate regression *P*-value <0.10 were included and subsequently removed if the Wald test *P*-value was >0.05. All results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and a two-tailed *P*-value ≤ 0.05 considered significant (χ^2 distribution *P*-value with 1 degree of freedom). Total prevalence of clinically significant (moderate or severe) VHD was obtained by combining data on newly diagnosed and pre-existing VHD (assuming that moderate or severe VHD would result in a clinical diagnosis). To derive population projections for significant VHD, we applied our age-specific prevalence data to Office of National Statistics projections (based upon the 2012 UK census) using gender-specific 5-year age-bands.

Results

Demography

Initial screening of primary healthcare records in study centres demonstrated that 2.9% of potential participants aged 65 years and older were deceased, 3.1% were no longer registered with the practice, and 4.9% had a pre-existing diagnosis of VHD. A further 13.2% were excluded from the echocardiographic study for other reasons (e.g. cognitive decline, terminal non-cardiac disease, or severe immobility). Study uptake among the remaining potential study population in the first practice to complete recruitment was 53%, consistent with previous community-based echocardiographic screening studies for cardiovascular disease (Supplementary material online, *Figure S1*).[10,11]

In the first 2500 enrolled participants, the mean age (SD) was 73 (6) years and 51.5% were female (*Table 1*), consistent with the demographics of the wider community population—UK 2011 Census data indicate that the mean age of the entire Oxfordshire population aged 65 years and older is 75.3 years (55.8% female). Almost all the study participants were of White ethnic background (99%)

Table 1 Demographics of study participants with and without valvular heart disease

	No VHD (SD or % of those with condition)	VHD (SD or % of those with condition)	*P*-value
Number of participants	1231 (49.2%)	1269 (50.8%)	
Age (years)	71.8 (5.3)	74.2 (6.5)	<0.001
Gender			
Male (%)	612 (50.5%)	600 (49.5%)	
Female (%)	619 (48.1%)	669 (51.9%)	0.239
Smoking status			
Non-smoker	586 (47.6%)	646 (52.4%)	
Ex-smoker	544 (49.7%)	550 (50.3%)	
Smoker	101 (58.0%)	73 (42.0%)	0.032
Socioeconomic class			
1 (least deprived)	647 (51.7%)	605 (48.3%)	
2	280 (50.1%)	279 (49.9%)	
3	207 (47.9%)	225 (52.1%)	
4 or 5 (most deprived)	97 (37.9%)	159 (62.1%)	<0.001
NYHA class			
I/II	1196 (49.1%)	1240 (50.9%)	
III/IV	35 (54.7%)	29 (45.3%)	0.449
History			
Diabetes mellitus	143 (50.7%)	139 (49.3%)	0.645
Hypertension	508 (45.2%)	615 (54.8%)	<0.001
Hyperlipidaemia	413 (46.3%)	479 (53.7%)	0.032
Atrial fibrillation	35 (32.1%)	74 (67.9%)	<0.001
Myocardial infarction	51 (38.9%)	80 (61.1%)	0.02
Coronary angiography	86 (38.4%)	138 (61.6%)	<0.001
Percutaneous coronary intervention	42 (43.3%)	55 (56.7%)	0.276
Coronary artery bypass grafting	15 (31.9%)	32 (68.1%)	0.024
Angina	101 (47.4%)	112 (52.6%)	0.628
Stroke/TIA	60 (38.7%)	95 (61.3%)	0.009
Rheumatic fever	20 (44.4%)	25 (55.6%)	0.618
Examination			
Heart rate (bpm)	73.9 (11.9)	71.7 (11.7)	<0.001
Systolic blood pressure (mmHg)	138.5 (18.9)	141.5 (19.9)	<0.001
Diastolic blood pressure (mmHg)	79.9 (11.3)	79.1 (11.2)	0.099
Ankle oedema	163 (53.4%)	142 (46.6%)	0.132
Body mass index (kg/m^2)	27.9 (4.9)	27.3 (5.1)	0.002

Results are presented as mean (SD) for continuous variables and numbers (%) for categorical variables, with percentage by row for each category. *P*-value is for *t*-test (continuous) and χ^2 or Fisher's exact test (categorical) to assess independence of VHD from each characteristic/condition. AF, current or previous atrial fibrillation; NYHA, New York Heart Association; TIA, transient ischaemic attack; VHD, valvular heart disease.

and relatively affluent, reflecting the demography of England and Wales, where 95% aged ≥65 years are of White ethnicity.[12] Similarly, the socioeconomic status of the study cohort (assessed by mean IMD score) was comparable with that of Oxfordshire as a whole (OxVALVE cohort 11.68, Oxfordshire 12.26).[13]

The vast majority (97.4%) of the study cohort (excluding those with known VHD) had minimal or no symptoms with only 2.6% (65/2500) in New York Heart Association Class III/IV.

Prevalence of valvular heart disease

Overall

Newly detected (predominantly mild) VHD was identified in just over half (50.8%) of this large asymptomatic population (*Table 2*, *Figure 1*). The most common valve lesion was AoScl (34% of those with newly detected VHD), followed by mitral regurgitation (MR; mild 19.8%, moderate/severe 2.3%) and aortic regurgitation (AR; mild 13.6%, moderate/severe 1.6%). Aortic stenosis (AS), the

Table 2 New diagnosis of valvular heart disease

	None/trivial	Mild	Significant (moderate/severe)
Any VHD	1231 (49.2%)	1110 (44.4%)	159 (6.4%)
Left-sided VHD			
Mitral regurgitation	1948 (77.9%)	494 (19.8%)	58 (2.3%)
Mitral stenosis	2491 (99.6%)	7 (0.3%)	2 (0.1%)
Aortic regurgitation	2118 (84.7%)	341 (13.6%)	41 (1.6%)
Calcific aortic valve disease—AoScl and stenosis	1617 (64.7%)	866 (34.6%)[a]	17 (0.7%)
	None/Trivial/Mild	**Significant (moderate/severe)**	
Right-sided VHD			
Tricuspid regurgitation	2433 (97.3%)	67 (2.7%)	
Pulmonary regurgitation	2493 (99.7%)	7 (0.3%)	

Number of study participants (% of total cohort) with newly diagnosed VHD (there were no cases of tricuspid or pulmonary stenosis). VHD, valvular heart disease.
[a] Mild calcific aortic valve disease refers to the combined number with AoScl and mild aortic stenosis.

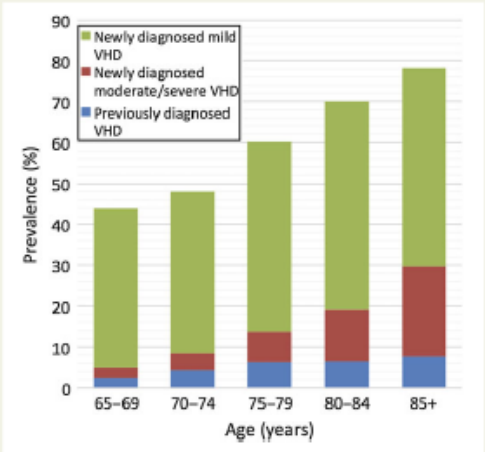

Figure 1 Population prevalence of valvular heart disease according to age.

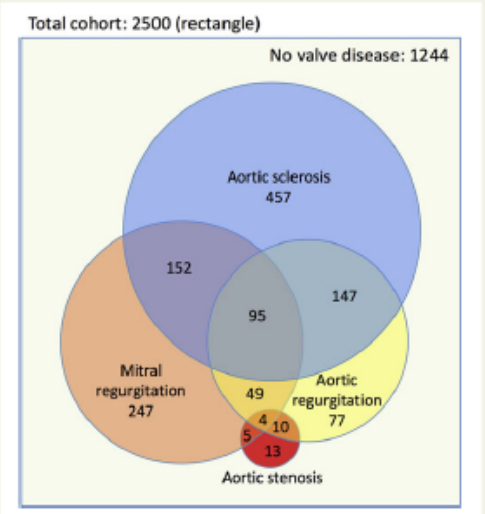

Figure 2 Venn diagram demonstrating the distribution of single and multiple left-sided valve abnormalities in OxVALVE participants with newly diagnosed valvular heart disease. The outer rectangle represents the full cohort ($n = 2500$) and the area of each circle is proportionate to the number of participants with different manifestations of left-sided valvular heart disease. Numbers denote the number of participants in each group.

most prognostically significant manifestation of VHD, was newly diagnosed in 1.3% of participants at a mean age of 77.3 (7.0) years in men and 75.6 (7.2) years in women. A bicuspid aortic valve (BAV) was found in only 8 (0.3%) participants, reflecting the age of the study cohort, and the fact that clinical manifestations of this condition usually present in the fifth or sixth decades.

Clinically significant valvular heart disease

Clinically significant (moderate or severe) VHD was newly diagnosed in 6.4% of participants. Addition of the further 4.9% of subjects with pre-existing VHD from the overall study cohort (assuming that moderate or severe VHD would result in a clinical diagnosis) created a derived total population prevalence of moderate or severe VHD of 11.3%.

Right-sided valvular heart disease

Significant right-sided VHD was less common. In addition to moderate–severe tricuspid regurgitation (2.7%), moderate pulmonary

regurgitation was found in 7/2500 participants (0.3%). There were none with tricuspid or pulmonary stenosis.

Multivalve disease

Multiple valve lesions were identified in over one-third (38.5%) of the study population, affecting 47% of those with AoScl, 58% with MR, and 81% with AR (*Figure 2*).

Association with clinical variables and socioeconomic class

Participants with newly detected VHD were on average 2.4 years older than those without (*Table 1*) and prevalence increased linearly with age, from 42.4% (379/894) in those aged 65–69 years to 76.3% (103/135) in those aged 85–95 years (*Figure 1*). The proportion with moderate or severe VHD was 3.3% (54/1621) amongst those aged 65–74 years, rising to 11.9% (105/879) in those aged ≥75 years.

We explored associations with clinical characteristics using multiple regression (*Figure 3A*, Supplementary material online, *Table S1*). After removal of non-significant variables, VHD was associated with older age, more deprived SEC, current or previous atrial fibrillation (AF), and higher systolic blood pressure. There was no association with gender. Conversely, current smoking, higher heart rate, diastolic blood pressure, and body mass index were associated with a lower prevalence of VHD.

Restricting this analysis to subjects with newly diagnosed clinically significant (moderate or severe) VHD, there was an association with older age, current or previous AF, prior smoking, and lower body mass index (*Figure 3B*). In this smaller subset, there was no SEC association.

A history of current or previous AF was present in 109 participants (4.4% of the total study population) and independently associated with both a new diagnosis of VHD of any severity (OR 1.85, 95% CI 1.18–2.89) and clinically significant (moderate or severe)

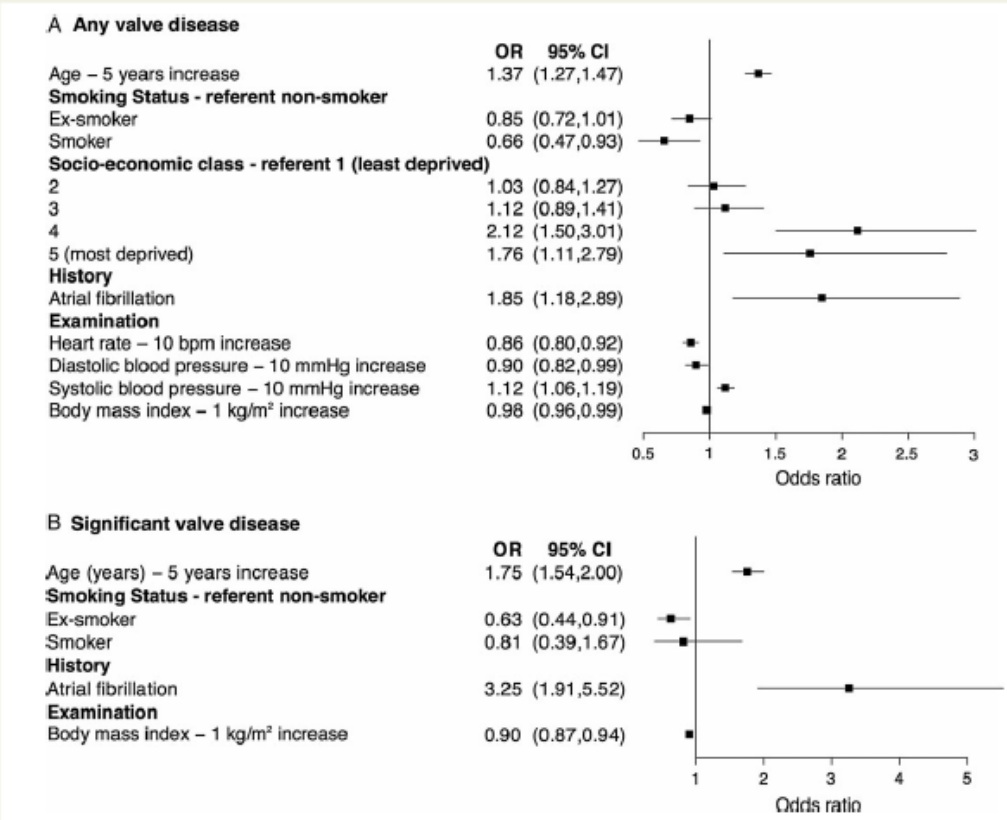

Figure 3 Clinical variables associated with a new diagnosis of valvular heart disease. Forest plot of odds ratios from multiple regression analysis of clinical associations with (*A*) any valvular heart disease, and (*B*) significant (moderate/severe) valvular heart disease. Only statistically significant variables are shown. Dots represent the odds ratio and whiskers represent the 95% confidence interval. CI, confidence interval; OR, odds ratio; SEC, socioeconomic class, according to national quintile.

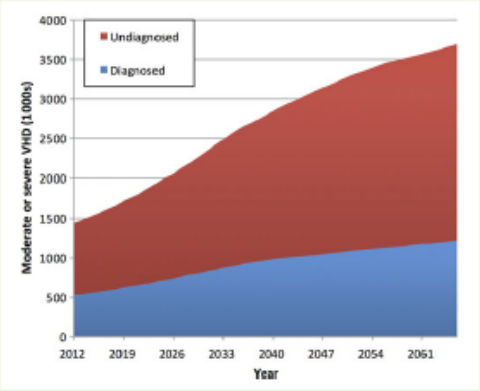

Figure 4 UK population projections of diagnosed and undiagnosed significant valvular heart disease. Diagnosed estimates are based on the number excluded from participation in the present study due to a prior diagnosis of valvular heart disease. Undiagnosed estimates are based on the number with newly diagnosed significant valvular heart disease in OxVALVE-PCS.

VHD (OR 3.25, 95% CI 1.91–5.52, $P < 0.001$; *Figure 3*). Moreover, participants with AF had a much higher prevalence of VHD than those in sinus rhythm (newly diagnosed VHD 67.9 vs. 32.1%; clinically significant [moderate or severe] VHD 21.1 vs. 5.7%), principally related to increased frequency of MR (mild 33.9 vs. 19.1%; moderate or severe 5.5 vs. 2.2%) and AR (mild 22.0 vs. 13.3%; moderate or severe 3.7 vs. 1.6%). By comparison, there was little difference in the frequency of AoScl (38.8 vs. 34.7%) or aortic stenosis (1.9 vs. 1.2%) between these groups. There were no participants with both AF and mitral stenosis in this Western European population.

Population projections

Combining our data concerning pre-existing and newly diagnosed VHD (and assuming no change in age and gender-specific prevalence), we predict a substantial rise in the clinical impact (and financial consequences) of clinically significant (moderate or severe) VHD within the rapidly expanding elderly population (*Figure 4*). The OxVALVE-PCS data suggest that the number of individuals in the UK aged 65 years or older with moderate or severe VHD will increase from 1.5 million in 2015 to 3.3 million in 2056 (122% increase), with a doubling in prevalence by 2046.

Discussion

The OxVALVE Population Cohort Study is the first population-based study of VHD worldwide and demonstrates both the prevalence of undiagnosed and known VHD in older people and the contemporary clinical and epidemiological characteristics of VHD. Previously undetected VHD was detected in just over half of 2500 participants and prevalence increased linearly with age. The total prevalence of clinically significant VHD was 11.3% when we included subjects with known VHD from the overall population cohort.

Previous studies addressing the prevalence of VHD have either been retrospective,[4,5] hospital-based,[3] or developed primarily to examine non-VHD.[14] Consistent with these, we demonstrated a significant increase in the prevalence of VHD with age.[3–5,15–17] A previous North American meta-analysis demonstrated that the prevalence of moderate or severe left-sided VHD was <1, 9.9, and 13.2% in those aged 18–44 years, >65 years, and >75 years, respectively.[4] Similarly, the prevalence of undiagnosed moderate/severe VHD in those aged ≥75 years in OxVALVE-PCS was 11.9%. Moreover, we excluded 4.9% of the overall potential community cohort (6.8% of those aged ≥75 years) from our echocardiographic study on account of a previous diagnosis of VHD. Although ethical constraints restricted access to more detailed information concerning this group, we can reasonably assume that most (if not all) of this VHD was clinically significant, providing an 11.3% total prevalence of significant VHD in the elderly population aged 65 years or older (18.7% of those aged ≥75 years). These figures are significantly higher than estimated in a previous meta-analysis.[4] A new diagnosis of moderate or severe VHD remains clinically important and should prompt specialist referral for evaluation, treatment, and/or long-term surveillance.

Aortic sclerosis, defined as thickening and focal calcification of the aortic valve leaflets without obstruction to flow, is a frequent incidental echocardiographic finding. Prevalence increases linearly with age and is estimated at 20–40% in the population aged >65 years.[18] Consistent with this, AoScl was detected in one-third of participants in the present study and was the most common manifestation of VHD. Although progression of AoScl to AS is slow and affects only a minority of individuals,[19,20] it is now accepted that AoScl is associated with adverse outcome over long-term follow-up and an independent marker of cardiovascular risk.[21,22] While ongoing research is addressing underlying mechanisms, vigorous vascular risk factor management combined with scheduled clinical and echocardiographic follow-up to monitor potential progression to significant AS is appropriate for individuals with AoScl identified in the context of cardiovascular screening or other echocardiographic assessment.

Aortic stenosis is associated with reduced life expectancy and carries a poor prognosis following the onset of symptoms. Aortic valve replacement and transcatheter aortic valve implantation are associated with significant reduction in mortality and morbidity, even in the very elderly.[23] Early identification of AS remains an important priority to avoid excess morbidity and mortality, even in the oldest population cohorts, and we were able to detect AS in 1.3% of our study population. Although BAV was historically reported in 1–2% of live births, more recent studies suggest that the prevalence is lower at 0.5–0.8%,[24–27] consistent with the prevalence of 0.3% in OxVALVE-PCS (particularly since those with a known BAV would have been excluded from our echocardiographic study).

Multivariate analysis confirmed a number of expected findings, such as the association of VHD with increasing age, current or previous AF, and elevated systolic blood pressure. While initially counterintuitive, lower BMI has previously been associated with higher prevalence of regurgitant valve lesions, perhaps due the increased ease of echocardiographic imaging in thin individuals.[17]

Although current smoking was associated with less VHD, a concurrent history of coronary heart disease (CHD) may have been an important confounding variable. Both current and ex-smokers were more likely to have CHD (Supplementary material online, *Table S2*) and previous echocardiography demonstrating associated VHD would have led to exclusion of this group from our echocardiographic study.

Variation in the prevalence and outcomes of coronary artery disease and stroke according to SEC is well described[28] but OxVALVE-PCS demonstrates an association between SEC and VHD for the first time. While this finding should be interpreted with caution given the relatively small sample sizes, the rate of VHD in the two most deprived groups (SEC 4/5) was approximately double that in the least deprived group (SEC 1, *Figure 3*). This association is not readily explained but could reflect a higher burden of unmeasured risk factors, such as exposure to passive smoking, or the small but measureable association between SEC and markers of ageing.[29] Consistent with local demographics, SEC 1 accounted for 50% of our cohort—larger, more diverse studies to analyse inequalities in the prevalence of VHD are warranted. At a practical level, there is a need to devise strategies to enhance access to specialist care in less affluent communities to facilitate the earlier diagnosis of VHD.

We identified current or previous AF as the clinical variable most strongly associated with newly diagnosed clinically significant (moderate or severe) VHD. These participants had a more than threefold increase in the likelihood of newly diagnosed clinically significant VHD. Although international guidelines indicate the need for initial echocardiography in all patients with AF,[30,31] recent recommendations from the UK National Institute for Health and Care Excellence reaffirm previous guidance that routine echocardiography is unnecessary.[32] Our data indicate that AF is an important and easily identifiable marker of silent VHD in asymptomatic individuals in primary care and that auscultation and routine echocardiography are appropriate. Anticoagulation is also of potential importance in this cohort, although none of the OxVALVE-PCS participants had a mechanical valve or mitral stenosis with associated AF (the two conditions known to independently increase thromboembolic risk in the setting of AF,[33] and for which novel oral anticoagulants are unlicensed).

The unique OxVALVE-PCS cohort will provide a platform for future studies examining long-term outcomes and cross-sectional associations of VHD in its earliest stages, enabling accurate assessment of the rate of progression in the community, exploration of genetic and biomarker associations, and elucidation of factors involved in the pathogenesis of this increasingly common condition.

Limitations

The present study has inevitable limitations. Although uptake was over 50% (despite ethical constraints permitting mail only contact with potential participants) and compatible with similar community-based studies,[10,11] selection bias with over-representation of motivated healthy individuals is possible.[34] Thus, although it is likely that the pragmatic exclusion of the infirm or those with cognitive decline will have skewed the data to an indefinable extent, this will, if anything, have led to an underestimation of the considerable population burden of VHD. Indeed, previous studies amongst nursing home residents have demonstrated very high levels of VHD.[35,36]

The Oxfordshire population is relatively homogeneous and our study population lacks ethnic and socioeconomic diversity, which makes it difficult to generalise our findings to other communities. This is, of course, a problem faced by other similar clinical studies. For example, a recent US study demonstrated a far lower rate of aortic stenosis in African Americans compared with Caucasians but equal rates of severe mitral regurgitation.[37] However, other key epidemiological series[5,17] have been similarly homogeneous despite being population-based, while other important studies[16] were limited to single ethnic groups. Although there have been numerous changes in European population dynamics in recent decades, a traditional ethnic structure prevails in older cohorts. For example, UK 2011 Census data demonstrate an equivalent or higher prevalence of White ethnicity compared with the OxVALVE cohort (98.8%) in 71/174 counties in England and Wales and prevalence of 95% or more in 120/174 counties.[12] Comparison with other European nations is difficult, although Dutch data indicate that 97% of those aged 65 and over in Holland are of Western origin,[38] suggesting that the Oxfordshire population is reasonably representative of other elderly Western European populations.

We also recognize that our study cohort (mean IMD score 11.68) and the overall Oxfordshire population (mean IMD score 12.26) is relatively affluent in comparison with the wider UK South East region (mean IMD score 14.75) or large cities such as London (mean IMD score 25.22) where multi-ethnicity and immigrant communities are likely to contribute to a greater prevalence of rheumatic valve disease. Comparison of our cohort with other UK populations would be of value and such collaborative studies are planned within our future research programme.

Conclusions

The OxVALVE Population Cohort Study is the first population-based study worldwide aimed specifically at the community detection of VHD. In a large cohort of 2500 elderly subjects we demonstrate a high prevalence of previously unidentified VHD and infer that the number of individuals with clinically significant VHD will increase substantially over the next five decades. The novel finding of increased VHD in more deprived socioeconomic groups (even in a high-income country such as the UK) places VHD among the group of diseases that disproportionately affects the poor. Furthermore, we demonstrate that clinically significant VHD is three times more common in individuals with current or previous AF, which provides an important and easily identifiable marker of silent VHD in asymptomatic individuals. These data are important for researchers and clinicians in enabling improved understanding of the pathophysiology, risk factors, and natural history of VHD, and for healthcare policy-makers and economists as the size of the elderly population and their health expectations increase, and expensive percutaneous treatment options emerge as an evidence-based alternative to conventional valve surgery.[39,40]

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Valvular Heart Disease

Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification

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Background—Surgery for severe mitral regurgitation is indicated if symptoms or left ventricular dilation or dysfunction occur. However, prognosis is already reduced by this stage, and earlier surgery on asymptomatic patients has been advocated if valve repair is likely, but identifying suitable patients for early surgery is difficult. Quantifying the regurgitation may help, but evidence for its link with outcome is limited. Cardiovascular magnetic resonance (CMR) can accurately quantify mitral regurgitation, and we examined whether this was associated with the future need for surgery.

Methods and Results—One hundred nine asymptomatic patients with echocardiographic moderate or severe mitral regurgitation had baseline CMR scans and were followed up for up to 8 years (mean, 2.5±1.9 years). CMR quantification accurately identified patients who progressed to symptoms or other indications for surgery: 91% of subjects with regurgitant volume ≤55 mL survived to 5 years without surgery compared with only 21% with regurgitant volume >55 mL (P<0.0001). A similar separation was observed for regurgitant fraction ≤40% and >40%. CMR-derived end-diastolic volume index showed a weaker association with outcome (proportions surviving without surgery at 5 years, 90% for left ventricular end-diastolic volume index <100 mL/m² versus 48% for ≥100 mL/m²) and added little to the discriminatory power of regurgitant fraction/volume alone.

Conclusions—CMR quantification of mitral regurgitation was associated with the development of symptoms or other indications for surgery and showed better discriminatory ability than the reference-standard CMR-derived ventricular volumes. CMR may be able to identify appropriate patients for early surgery, with the potential to change clinical practice, although the clinical benefits of early surgery require confirmation in a clinical trial. (***Circulation***. **2016;133:2287-2296. DOI: 10.1161/CIRCULATIONAHA.115.017888.)**

Key Words: magnetic resonance imaging ■ mitral valve ■ mitral valve insufficiency ■ outcome assessment (health care) ■ prognosis

Mitral regurgitation (MR) is usually well tolerated, and even those patients with severe asymptomatic regurgitation can survive many years, although about a third develop indications for surgery by 5 years.[1] Mitral valve repair or replacement is indicated once symptoms or adverse cardiac features develop[2] (eg, left ventricular [LV] dysfunction/excess dilation) because prognosis is significantly worse without treatment.[3–5] However, even with surgery, prognosis may be worse at this stage, and early surgery for severe regurgitation has been advocated.[6,7] The latest guidelines now consider this to be reasonable (Class IIa indication) if severe MR is present, the chance of mitral repair is high (>95%), and the surgery is carried out in a center of excellence with a very low mortality or other conditions exist (pulmonary hypertension or new-onset atrial fibrillation).[2] This aggressive approach has to be balanced against the favorable natural history of untreated MR without symptoms or other adverse features and the risks of early surgery, particularly in an elderly population in whom the risks of surgery are higher. There is therefore considerable debate between those who advocate a "watchful waiting" strategy[1] and those who favor early surgery.[8,9] Determining the correct clinical approach is hindered by the lack of any controlled trial of early surgery and the difficulty in identifying which patients should be offered surgery while asymptomatic. Advance identification of those patients likely to progress to symptoms or other indications for surgery in the near future

Clinical Perspective on p 2296

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could highlight the group most likely to benefit and facilitate early surgery before the prognosis is worsened.

Quantifying the MR in those with significant regurgitation (rather than qualitative grading) might be one method to identify such patients. This can be achieved with echocardiography,[10] although echocardiographic quantification is used primarily to aid grading as mild, moderate, and severe regurgitation[10] rather than identifying patients for surgery. One important study has shown an association of quantitative echocardiographic MR grading with mortality in medically treated patients,[11] but this study did not address the identification of patients for surgery.

Cardiovascular magnetic resonance (CMR) is able to quantify MR with high accuracy and reproducibility using a combination of LV volumetric measurements and aortic flow quantification with phase-contrast velocity mapping.[12] Given that LV volumes and function are also important for MR assessment and that CMR is considered the reference-standard method for measuring them,[13] CMR would appear to be an optimal technique for the assessment of MR. We previously used this technique in patients with aortic regurgitation and demonstrated a strong association of the quantification of regurgitation with outcome.[14] We therefore sought to examine whether a similar approach using CMR quantification of MR and LV indexes might be able to predict which asymptomatic patients with significant (moderate or severe) MR were likely to progress to symptoms or other established indications for surgery. We also aimed to compare the CMR quantification of MR and LV volume/function indexes for their relative predictive ability.

Methods

Subjects and Follow-Up

Patients at least 18 years of age were recruited from 4 high-volume CMR centers in Oxford, Leeds, London (UK) and Auckland (New Zealand). All asymptomatic patients with moderate or severe chronic organic MR on echocardiography were eligible for inclusion and underwent baseline CMR scanning. Exclusion criteria included the presence of functional MR (secondary to annular dilation or LV dysfunction), other significant valve disease, and clinical or angiographic evidence of coronary disease.

Subjects were followed up for up to 8 years. Those who remained asymptomatic and under conservative management were designated the conservative group; those who developed symptoms or other established indications for surgery[2] were designated the crossover group, with the decision for surgery taken as the point of censoring. Subjects were included in the crossover group only if the surgery was indicated on the basis of established criteria,[2] which do not include CMR assessment. Any subjects undergoing mitral valve replacement/repair for indications outside these criteria (including mitral repair performed for asymptomatic severe MR without other indications of adverse prognosis) remained in the conservative group but were censored at the time of surgery. In addition, a minimum period of 1 month was required between the CMR scan and the decision for surgery to avoid the potential bias of patients having a predesignated CMR scan en route to surgery. All clinical decisions were made by the treating physician. In Oxford, patients participated in a research study, and clinical decisions were made without knowledge of the CMR data. In the other 3 centers, study patients were identified from the clinical CMR databases (having been initially diagnosed with echocardiography), and clinicians had access to the CMR data, although as indicated above, there are no CMR-based criteria for surgery.

A third group was also included to compare CMR parameters with both the conservative and crossover groups. This group included patients who had already developed established indications for surgery[2] and were scheduled for mitral valve repair/replacement (the surgical group). They underwent CMR scans identical to those of the other groups.

The research study was approved by the Oxfordshire Central Research Ethics Committee (project code C02.020) and the Waitemata District Health Board Knowledge Center in New Zealand (project No. RM0980711302). All research subjects gave written informed consent.

CMR Scanning

All scans were performed on clinical 1.5-T scanners (Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany; or Philips Intera, Philips Healthcare, Best, the Netherlands) and analyzed in each center with dedicated software (Argus, Siemens; CMR42, Circle Cardiovascular Imaging, Calgary, AB, Canada; or CMRtools, Cardiovascular Imaging Solutions, London, UK) for both volumes and flow according to standard acquisition guidelines.[12] All images were ECG gated, and most were obtained during an 8- to 16-second breath-hold to remove cardiac motion resulting from the respiratory cycle. Subjects underwent an LV function study consisting of a stack of contiguous short-axis cine images from base to apex, from which LV end-diastolic volume (LVEDV) and LV end-systolic volume and mass were measured, and LV stroke volume was derived as LVEDV minus LV end-systolic volume. Each value was also indexed to body surface area. Cine image sequences were steady-state free precession (temporal resolution, 35–45 milliseconds; echo time, 1.40–1.54 milliseconds; repetition time, 2.80–3.08 milliseconds; field of view, 380×380 mm; flip angle, 50°–60°).

Aortic forward flow was quantified with through-plane phase-contrast velocity mapping as previously described,[15,16] with the image plane placed either just above the aortic valve at end diastole or at the sinotubular junction (Figure 1). If significant turbulence or aliasing was seen in the velocity image, the acquisition was repeated a few millimeters further from the valve or with a higher-velocity window. Free-breathing flow sequences were used in Oxford; breath-hold flow sequences were used in the other 3 centers. Our previous work has shown that the choice of pulse sequence (free breathing versus breath hold) does not significantly affect the quantitative results.[14] In all centers, the potential for background flow offset errors was reduced[17] by ensuring that flow sequences were acquired with the region of interest located at the isocenter of the magnet to minimize any inhomogeneities in the magnetic field. Image parameters were as follows: temporal resolution, 25 to 55 milliseconds; echo time, 2.6 to 3.2 milliseconds; repetition time, 4.3 to 7.8 milliseconds; field of view, 320×320 mm; velocity window, 2.0 to 2.5 m/s; signal averages, 1 for breath-hold sequences and 3 for free-breathing sequences; and typical acquisition times, 12 to 16 seconds for breath-hold sequences and 2 to 3 minutes for free-breathing sequences.

Standard CMR quantification of MR involves the deduction of aortic flow from LV stroke volume (aortic forward flow). In the absence of interventricular shunting, this equates to the volume of MR. This technique is robust in the presence of changing degrees of MR during systole, in addition to eccentric or mobile mitral regurgitant jets. Regurgitant fraction was also determined (regurgitant volume/LV stroke volume×100%).

Echocardiography

Transthoracic echocardiograms were acquired for clinical management a mean of 47.1±71.6 days from the baseline CMR scan, according to standard protocols.[18] The images for the subjects who were prospectively followed up (conservative and crossover groups) were reassessed by the researchers who were blinded to CMR and outcome data, and determination of the grade of MR on echocardiography was made. This determination was based on multiple 2-dimensional imaging parameters, as described in the American Society of Echocardiography guidelines.[10] These were both qualitative and semiquantitative, and quantitative assessments were used whenever

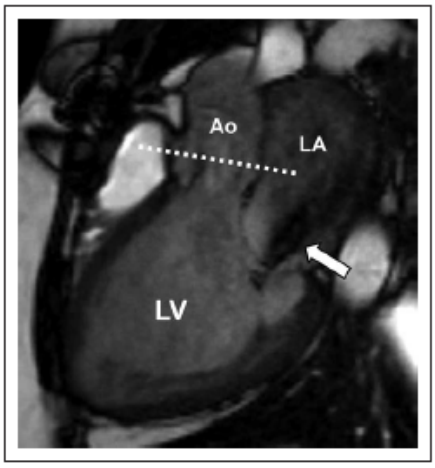

Figure 1. Cardiovascular magnetic resonance flow measurement in mitral regurgitation. Still frame from steady-state free precession cine showing left ventricular outflow tract view in systole with the mitral regurgitation jet (arrow) and the slice location for aortic (Ao) through-plane flow measurement (dashed line). Mitral regurgitant volume is calculated left ventricular (LV) stroke volume minus aortic forward flow. LA indicates left atrium.

feasible (including assessment of effective regurgitant orifice area by the proximal isovelocity surface area [PISA] method[19]) if accurate measurements could be obtained.

Data Assessment and Statistical Analysis

Receiver-operating characteristic analysis was used as the initial test to identify the imaging parameters with a reasonable ability to identify patients who would develop symptoms or other indications for surgery during follow-up. The optimal threshold for sensitivity and specificity was determined from the Youden index. Stepwise Cox proportional hazards regression analysis was also performed on these parameters to determine which were independent predictors.

Kaplan–Meier survival curves are more appropriate for assessing the occurrence of events over time and were generated for parameters with a receiver-operating characteristic area under the curve >0.70 to identify the strongest predictors. There are, however, no existing CMR thresholds for regurgitation severity to determine the subgroups for comparing progression over time. In addition, it is likely that there is an increasing (continuous) risk with increasing regurgitation/ventricular size, and a single threshold may not necessarily be appropriate. To determine the best cutoff thresholds for separating groups, Cox proportional hazards assessment was used, with each parameter investigated separately in a univariate Cox model. The factors were dichotomized at different cutoff levels, and discrimination was assessed by the Harrell C and Somers D statistics. The cutoff thresholds with the highest Harrell C and Somers D statistics were used to separate groups in the survival analyses.

All analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL) except the receiver-operating characteristic analyses, which were performed with MedCalc version 9.3.1 (MedCalc Software, Mariakerke, Belgium), and the Cox proportional hazards assessment of different cutoff thresholds, which was performed in R version 3.2.3. Values shown are mean±SD. A value of $P<0.05$ was considered the threshold for statistical significance.

Results

One hundred nine asymptomatic patients with at least moderate MR on echocardiography were included in the study and followed for up to 8 years (mean±SD, 2.5±1.9 years; median, 1.6 years; 25th and 75th percentiles, 0.8 and 3.5 years). Twenty-five patients (23%) underwent mitral valve repair/replacement during the follow-up period (crossover group), having developed symptoms (n=19) or other established echocardiographic indications for surgery (excessive LV dilation [end-systolic diameter >4.0 cm], n=4; or pulmonary hypertension [>50 mm Hg] with a repairable valve, n=2). The mean time from CMR scan to the decision on surgery in this group was 1.9 years (median, 1.1 years; 25th and 75th percentiles, 0.4 and 3.0 years), with 85% of events occurring within 4 years. Seven patients underwent mitral surgery but did not have conventional indications. They remained in the conservative group but were censored at the time of surgery. The surgery in these 7 subjects was mainly mitral repair for severe MR but without clear indications of adverse prognosis; the mean regurgitant fraction was 36% (range, 26%–56%).

Association With the Need for Surgery

The receiver-operating characteristic analyses identified several baseline CMR parameters that were associated with the development of indications for surgery (Table 1). Quantitative measures of MR (mitral regurgitant volume and fraction) had a high area under the curve with good sensitivity and specificity. CMR LV volumetric indexes also showed good discriminatory ability. LV mass showed some predictive power, but this parameter is closely related to LVEDV, and the similar mass-to-volume ratios in all groups (Table 2) suggest that LVEDV is likely to be the main determinant of LV mass. Cox regression analysis showed independent associations for regurgitant volume (b exponent, 1.03 [95% confidence interval, 1.01–1.05] per 1-mL increase; $P=0.01$) and for regurgitant fraction (b exponent, 1.05 [95% confidence interval, 1.01–1.09] per 1% increase; $P=0.01$) if assessed separately from regurgitant volume. Otherwise, this was too closely related. Assessment of the best dichotomous cutoff threshold for discrimination of the need for surgery was performed for regurgitant volume, regurgitant fraction, and LVEDV index (LVEDVi). For regurgitant volume, cutoff levels between 30 and 65 mL were analyzed with Cox proportional hazards, and the highest values of the Harrell C and Somers D statistics were associated with a cutoff threshold of 55 mL. For regurgitant fraction, cutoff levels between 20% and 50% were investigated, and the optimum cutoff level was 40%. For LVEDVi, cutoff levels between 80 and 130 mL/m^2 were investigated, and the optimum cutoff level was 100 mL/m^2. These thresholds were then used to separate subgroups in the survival analyses.

CMR measures of regurgitation demonstrated substantial separation of groups over time. Subjects with a regurgitant volume ≤55 mL had a very high chance of remaining free of symptoms or surgery: 95% at the median time (1.6 years) and 91% at 5 years. This contrasted with 54% at 1.6 years and 21% at 5 years for patients with regurgitant volume >55 mL ($P<0.0001$ by log rank; Figure 2A). Similar differences in survival without surgery were seen for regurgitant fraction >40% and ≤40%. However, inclusion of an additional threshold at a regurgitant fraction of 50% (dividing the cohort into 3 subgroups of ≤40%, 41%–50%, and >50%) revealed a further separation in survival without surgery, and we have illustrated

Table 1. Receiver Operating-Characteristic (ROC) Data: Comparison of the Ability of Each CMR Parameter to Identify the Initially Asymptomatic Patients Who Would Develop Indications for Surgery

	AUC	Threshold	*P* Value for ROC Curve	Sensitivity, %	Specificity, %
Regurgitant volume, mL	0.81 (0.72–0.88)	>55	<0.0001	72	87
Regurgitant volume index, mL/m²	0.79 (0.70–0.87)	>29	<0.0001	78	82
Regurgitant fraction, %	0.79 (0.70–0.86)	>40	<0.0001	76	74
LVEDV index, mL/m²	0.75 (0.65–0.83)	≥95	<0.0001	91	56
LV mass, g	0.77 (0.67–0.85)	>171	<0.0001	74	73
LVESV index, mL/m²	0.71 (0.61–0.79)	>36	0.0008	74	68
LV ejection fraction, %	0.71 (0.61–0.79)	<65	0.0006	60	76
RV ejection fraction, %	0.62 (0.51–0.72)	<59	0.08	58	54

Threshold is the value for each parameter that best identified the crossover group with the Youden index used for optimal sensitivity and specificity. AUC indicates area under the curve; CMR, cardiovascular magnetic resonance; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; ROC, receiver-operating characteristic; and RV, right ventricular.

this incremental risk of surgery with increasing regurgitant fraction in Figure 2B. There were no significant differences in survival curves among the participating centers (P=0.80 by log-rank test).

LVEDV also showed a reasonable association with outcome over time, although slightly weaker than for measures of regurgitation (proportions surviving without surgery at the median of 1.6 years: 96% for LVEDVi <100 mL/m² versus 71% for ≥100 mL/m²; P=0.0001; Figure 2C). However, stratifying groups by LVEDV in addition to regurgitant volume in the survival analysis did not provide any further separation of the curves than those for regurgitant volume alone, which was a better predictor (Figure 3A). There were only 2 subjects with high regurgitant volumes (>55 mL) but lower LVEDVi (<100 mL/m²), suggesting that in almost all cases, once a high volume of MR was present, LVEDV was increased (as might be expected).

Echocardiographic grading of MR performed less well in predicting subjects who progressed to surgery despite the use of quantitative assessment to guide grading when feasible (n=53, 49% of the total). Many of those identified as having severe MR on echocardiography had MR volumes on CMR <55 mL and remained asymptomatic (n=28). There was a much smaller tendency to underestimate the MR with echocardiography (compared with CMR), with only 5 subjects with moderate MR on echocardiography and regurgitant volume >55 mL by CMR. Overall, if the CMR threshold of a regurgitant volume >55 mL is used to define severe MR, 33 subjects (30% of the total) were reclassified by CMR compared with echocardiographic grading. The prediction of events with the use of only quantitative echocardiographic thresholds for severity (effective regurgitant orifice area >0.40 and <0.40 cm²) showed only modest separation of survival curves (Figure 2D), although numbers in this subgroup were smaller (n=53) and the difference in outcome was not statistically significant. Using echocardiography-derived regurgitant volume >60 mL (the guideline threshold for severe MR) as the threshold provided very similar results (data not shown). Furthermore, in both the moderate and severe echocardiographic MR subgroups, there was a similar separation of survival curves by CMR quantification (Figure 3B). Sixty-five subjects had follow-up echocardiograms during the study period, which were also analyzed in the same blinded fashion as the initial studies. Nearly all had findings similar to the first scan, with only 1 subject who progressed to surgery showing a change in the grade of MR by echocardiography (from moderate to severe), but this may not be surprising given the tendency for the initial echocardiography to overestimate the severity of MR, highlighted above.

Comparison With the Surgical Group

Descriptive data from all groups, including the surgical cohort, are shown in Table 2. Statistical comparisons were not made between groups, however, because the time-dependent (ie, incomplete) nature of the separation into conservative and crossover groups would make this statistically inappropriate. The surgical cohort showed mean MR and LV volumetric indexes similar to those of the crossover group, and both parameters were larger than in the conservative group. There were no significant differences in ejection fraction or right ventricular (RV) parameters. Systolic blood pressure was lower in the surgical compared with the conservative group.

Discussion

The Association of MR Quantification With Outcome

Quantifying MR with CMR showed a strong association with the future need for surgery over the subsequent 5 years, demonstrating the potential value of this approach. Patients already destined for surgery (the surgical group) also had measures of MR that were similar to those of the crossover group, suggesting that a similar threshold of regurgitation had been reached in the surgical group before symptoms occurred. These CMR parameters might thus be useful clinical predictors of the need for surgery. In addition to the potential for high quantitative indexes of regurgitation to identify candidates for early surgery, subjects with lower amounts of MR (regurgitant volume ≤55 mL or fraction ≤40%) had a very low chance of requiring surgery over the subsequent few years and could be followed up less frequently, with a favorable impact on healthcare resources. We identified the best single thresholds to predict

Table 2. Comparison of CMR Parameters Between the 3 Groups of Patients With MR

	Conservative	Crossover	Surgical
Patients in group, n	84	25	43
Age, y	65.1±14.9	63.8±12.6	66.3±7.5
Male subjects, %	65	76	60
In atrial fibrillation, %	19	32	24
Height, cm	172.8±10.1	174.2±10.4	171.3±9.7
Weight, kg	74.8±12.0	75.8±10.6	75.2±14.1
Body surface area, m^2	1.88±0.18	1.89±0.24	1.91±0.17
Heart rate, bpm	68.5±13.9	67.3±10.3	73.0±13.8
Systolic BP, mm Hg	143.9±23.1	132.1±20.1	120.9±13.2
Diastolic BP, mm Hg	77.8±10.8	77.4±8.8	73.9±11.3
Regurgitant volume, mL	39.4±20.0	65.9±23.7	70.1±29.5
Regurgitant fraction, %	32.1±12.4	45.7±11.7	46.7±14.0
LVEDV, mL	182.7±50.3	224.3±47.8	229.1±49.4
LVEDV index, mL/m^2	97.9±25.1	117.5±23.0	122.1±23.8
LVESV, mL	62.1±26.1	81.8±29.0	82.7±36.7
LVESV index, mL/m^2	33.5±13.8	42.5±13.3	44.2±18.3
LV ejection fraction, %	66.9±7.6	63.9±7.4	64.9±9.3
LV mass, g	144.5±49.9	192.9±46.4	192.9±61.6
LV mass index, g/m^2	76.2±24.6	102.7±23.9	103.4±25.6
LV mass/LVEDV ratio, g/mL	0.83±0.27	0.89±0.17	0.87±0.23
Echocardiographic LVEDD, cm	5.4±0.8	6.2±0.5	6.1±0.8
Echocardiographic LVESD, cm	3.3±0.7	3.6±0.6	3.8±0.9
Echocardiographic ERO, cm^2*	0.58±0.75	0.57±0.28	
Echocardiographic regurgitant volume, mL*	74.3±73.9	89.3±35.8	
RVEDV, mL	149.1±45.1	147.2±36.3	154.8±40.7
RVESV, mL	66.8±25.7	68.0±26.8	71.4±27.4
RV ejection fraction, %	56.0±8.5	54.1±9.9	52.4±11.3

Values are mean±SD. Note that statistical comparisons are not made between groups because the time-dependent nature of the allocation to the conservative and crossover groups would make this inappropriate. BP indicates blood pressure; CMR, cardiovascular magnetic resonance; ERO, effective regurgitant orifice area; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; and RVESV, right ventricular end-systolic volume.

*n=53 for these 2 parameters.

the groups with different outcomes, but it is likely that there is an increasing risk with increasing values of the parameters, as the separation of the 3 groups for mitral regurgitant fraction illustrates (Figure 2B). The thresholds identified in this study should be treated with caution, however, because there are some important limitations to the study. The cohort was only a moderate size, and the lack of a separate validation cohort resulted in the optimal cutoff thresholds being derived from and applied to the same data set. The degree of separation between groups is therefore likely to be optimistic and may not be as strong in other studies/cohorts. For similar reasons, the value of the cutoff threshold should also be treated with caution, and a validation cohort is required to confirm these thresholds.

The separation of the Kaplan–Meier event curves was slightly less pronounced than in our previous work in aortic regurgitation,[14] which may be attributable to a number of factors. MR is partly dependent on nonvalvar factors (eg, fluid balance, filling pressures, LV function), and the quantity of MR may vary more widely over a period of time than aortic regurgitation. Thus, a single measurement may show a weaker link with outcome. Second, the CMR technique for quantification is indirect and relies on both LV stroke volume measurement and aortic forward flow quantification, introducing more potential for error, which could also weaken the association with outcome. The threshold of regurgitant fraction that best differentiated the groups likely to progress to surgery was also higher for MR (40% versus 33% for aortic regurgitation), which may reflect a greater ability of the LV to cope with MR before the development of symptoms, particularly as the additional volume load is ejected into the low-pressure left atrium rather than the high-pressure aorta. Our findings also suggest that the thresholds for identifying severe mitral and aortic regurgitation should differ. There are currently no CMR-specific thresholds, but the American Heart Association/American College of Cardiology echocardiographic thresholds indicating severe regurgitant volume (60 mL) and fraction (50%) are the same for both valve lesions.[2] Interestingly, these values are close to the thresholds for the best identification of future symptoms in the present study for both mitral regurgitant volume (55 mL) and fraction, especially with the higher rate of progression to symptoms with a regurgitant fraction >50% (Figure 2B). For aortic regurgitation, however, the American Heart Association/American College of Cardiology thresholds are somewhat higher than the optimal thresholds identified in our previous study (regurgitant fraction, 33%; or regurgitant volume, 42 mL), which may suggest that different thresholds for each valve lesion or CMR-specific thresholds should be considered.

Comparison With LV and RV Volumetric Indexes

The highly accurate measurements of LVEDV by CMR showed a reasonable association with survival without surgery over time, but regurgitation quantification showed a better separation of survival curves. Furthermore, combining LVEDV and regurgitant volume subgroups did not improve survival curves over regurgitant volume alone, and subjects with low regurgitant volumes (Figure 3A) had similarly low rates of surgery regardless of the LVEDVi. This suggests that LVEDV may partly be a function of the quantity of regurgitation (supported by the strong association of LVEDV with mitral regurgitant volume).[20] This would be logical given that regurgitation is the physiological stimulus for LV dilation in this patient group, although this is not conclusively proven with our data, and the fact that several subjects with higher

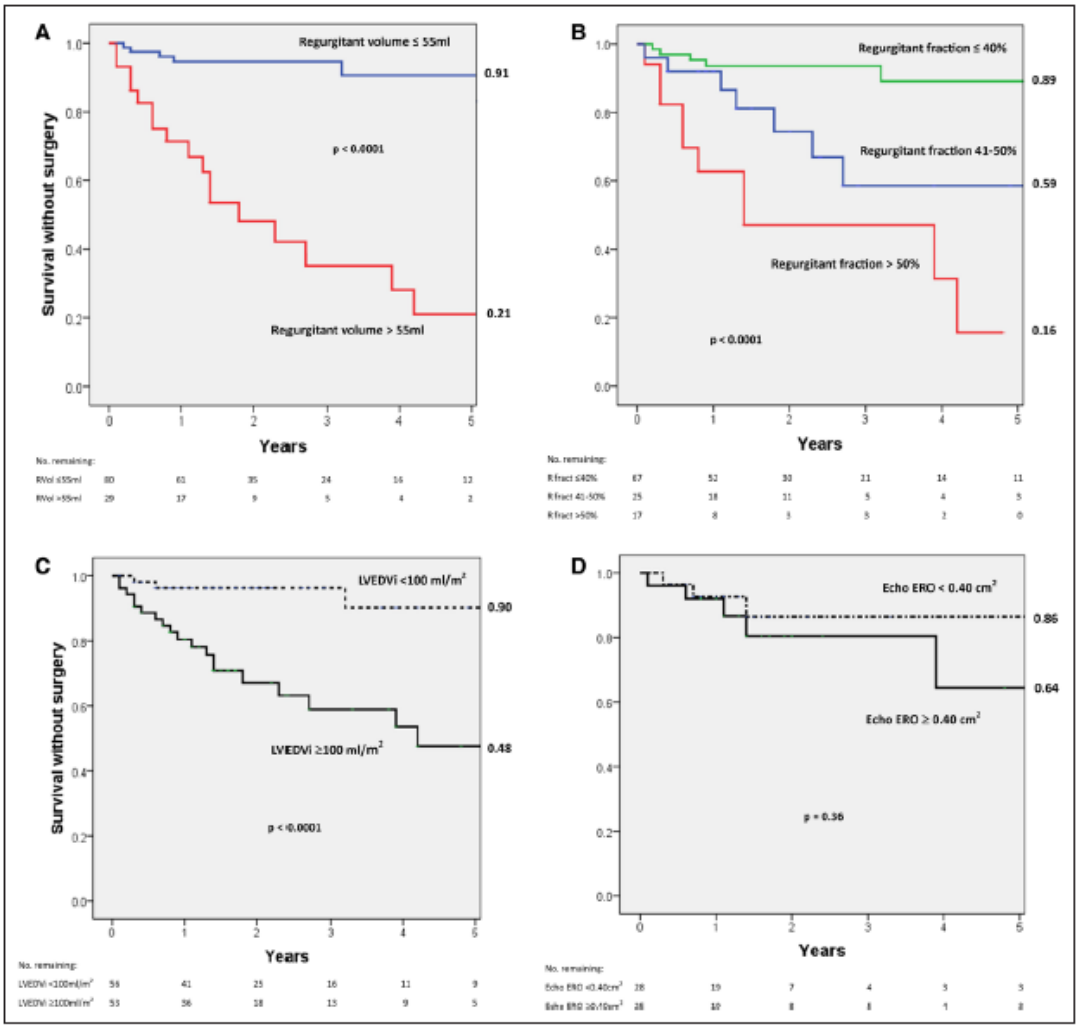

Figure 2. Surgery-free survival according to mitral regurgitant volume (RVol)/fraction (Rfract) and left ventricular end-diastolic volume index (LVEDVi). Kaplan–Meier graphs for survival without surgery in 109 asymptomatic subjects with at least moderate mitral regurgitation initially treated conservatively and followed up for up to 8 years stratified by cardiovascular magnetic resonance–derived (**A**) mitral regurgitant volume, (**B**) mitral regurgitant fraction, (**C**) LVEDVi, and (**D**) echocardiographic effective regurgitant orifice area (Echo ERO) <0.40 and ≥0.40 cm² (n=53 for this group).

LVEDVi had low regurgitant volume (Figure 3A) suggests that other factors influence LVEDV. Despite its long-standing use in previous guidelines, LV end-systolic volume did not have a particularly strong association with outcome. However, LV volumes and function are important in overall assessment and readily available from a standard CMR scan. LV mass showed an apparent association with progression to surgery, but this parameter is closely related to LV volume and was not an independent predictor. Other studies have not shown any predictive power of wall thickness,[21] and LV mass-to-volume ratios were similar for all 3 groups in our study, suggesting that there is no excess increase in mass over that required for the chamber volume increase and that the apparent association of LV mass with outcome is likely to be confounded by its close relation to LV volume. The lack of any notable association of RV parameters (including volumes and ejection fraction) with outcome, together with the similar (normal) values in all 3 groups, suggests that RV dilation or dysfunction may be a late and uncommon occurrence and may occur only secondary to LV dysfunction and the resulting pulmonary hypertension.

Systemic Blood Pressure

Systemic blood pressure was lower in the crossover and surgical groups, which may reflect the larger mitral regurgitant

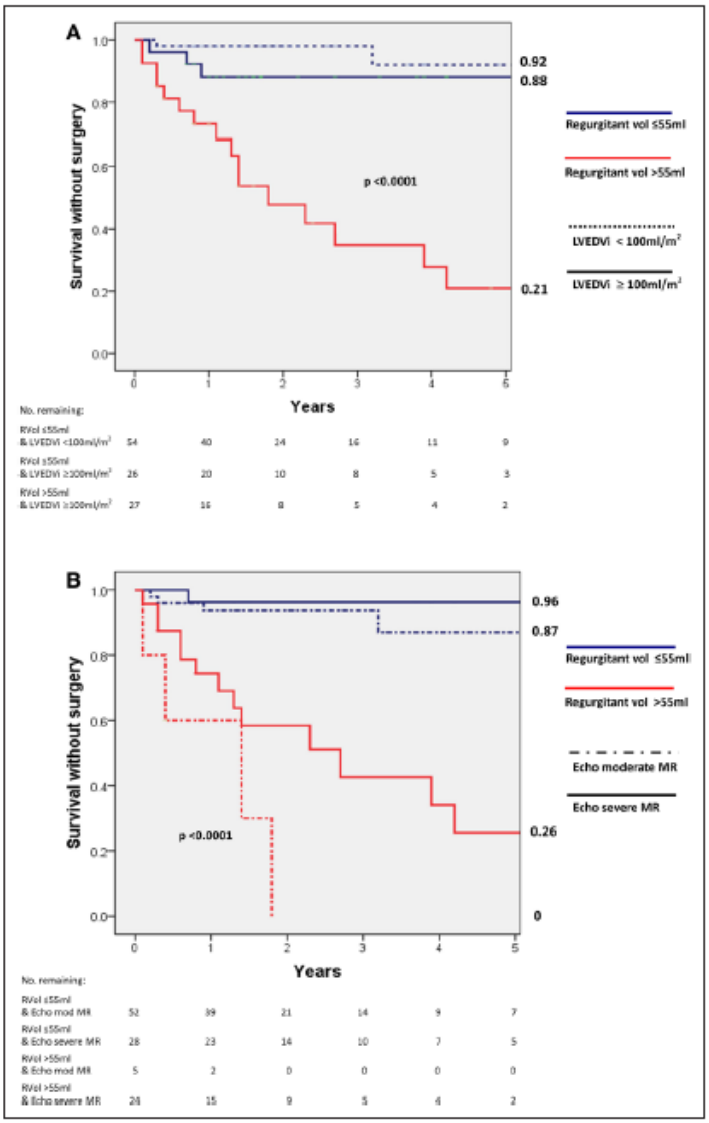

Figure 3. A, Surgery-free survival stratified by both cardiovascular magnetic resonance (CMR) regurgitant volume (RVol) and left ventricular end-diastolic volume index (LVEDVi; Note that there were too few subjects [n=2] with CMR regurgitant volume ≤55 mL and LVEDVi ≥100 mL/m², so this group was excluded). **B**, CMR regurgitant volume and echocardiographic mitral regurgitation (MR) grade. Note that the group with CMR regurgitant volume >55 mL and moderate MR on echocardiography contains only 5 subjects.

volumes (and reduced aortic forward flow) in these groups. It is possible the lower blood pressure was a confounding factor that might have increased the chance of developing indications for surgery, although no previous study has suggested a causal link between blood pressure and the need for surgery in MR. Furthermore, systolic blood pressure was not a good discriminator on the initial receiver-operating characteristic analysis (area under the curve=0.64).

Comparison Between Echocardiography and CMR

In our study, transthoracic echocardiographic grading showed a more modest ability to discriminate between subjects progressing to surgery and those remaining asymptomatic, with significant spread of the echocardiographic grades across the conservative and crossover groups and a tendency for echocardiography to overestimate the degree of regurgitation compared with CMR. However, we were able to apply quantitative echocardiographic grading in only ≈50% of subjects. Had this been possible in all subjects, it may have improved the results for echocardiography. Previous studies also suggest only moderate agreement between CMR and echocardiography[22–24] and limited reproducibility for quantitative echocardiographic grading.[25,26] This may be due in part to assumptions in the PISA technique (the commonest echocardiographic quantitative method). The peak PISA measurement assumes a static degree of regurgitation throughout

systole, and this may not hold true for some subjects, particularly those with mitral prolapse, which could result in overestimation of the degree of regurgitation.[27] Other aspects may also reduce the accuracy of PISA echocardiographic quantification, including irregular regurgitant jets (eccentrically directed, fan shaped/crescentic, or multiple), nonhemispheric geometry of the PISA shell, and difficulty in identifying the regurgitant orifice.[26–28] Although it is acknowledged there is no ideal gold standard for comparison, CMR quantification of regurgitation has shown better intraobserver and interobserver variability[29] and good agreement with in vitro models[23] and postsurgical LV remodeling.[24]

Previous Studies of Outcome in MR

Earlier studies examined outcomes after mitral valve surgery, demonstrating poorer 10-year survival after the development of symptoms[3] or LV impairment[4] and poorer postoperative LV function once preoperative end-systolic dimension exceeded 5.0 cm (an indicator of both dilation and reduced function).[30] These studies informed the current guideline indications for surgery in MR [2] and, like the present study, highlight the value of identifying patients before symptoms or significant LV dilation/dysfunction. Chronic MR also increases left atrial size and can raise pulmonary pressure, resulting in RV dysfunction. Both increased atrial size[21,31] and reduced RV or biventricular function[32] have been shown to predict medium- and long-term survival after mitral surgery. Reduced RV function on exercise has also shown some association with symptoms and outcome.[33,34] The lack of an association of RV function with future progression to surgery in our study might indicate that this is a late sign in decompensated MR, which is usually absent in an asymptomatic population such as ours (several of the previous studies involved patients with symptoms). We also did not assess RV function during exercise, and it is unclear whether this might explain some of the difference.

Few studies have predicted outcome (mostly progression to surgery) in an initially asymptomatic group of patients. The Mayo Clinic study[11] showed a significant association of quantitative echocardiographic grading with prognosis (both mortality and cardiac events), although this study did not specifically assess the progression to cardiac surgery, which was not included as a cardiac event. Subjects with moderate MR also had a significant cardiac event rate (40%, versus 62% for severe MR), which suggests a weaker ability of quantitative echocardiography to identify patients at risk of events, and highlights the difficulty in separating moderate and severe MR in some patients, the very group examined in our study.

Clinical Utility

Accurate assessment of the severity of MR and LV volumes/function is crucial in clinical decision making,[7] and CMR would already seem well suited for this. The additional ability to predict the onset of symptoms or other indications for surgery just before their occurrence would be clinically important and might identify a suitable cohort for careful surveillance and early surgery. Conversely, patients with less severe MR might be reassured of the good medium-term prognosis and require less frequent follow-up, thereby improving the efficient use of healthcare resources.

Observational studies have shown better outcomes in patients undergoing early surgery for MR,[6,35] but their limitations are well recognized. A randomized trial comparing early surgery with surgery based on conventional indications is required to demonstrate patient benefit, and our study may provide the basis for such a trial, with quantitative CMR indexes providing the appropriate tool for identifying suitable patients.

Limitations

The moderate sample size and relatively small number of events limit the strength of our conclusions, although follow-up was for a reasonable period of time (mean, 2.5 years; maximum, 8 years). Although the study suggests that CMR may be used to identify candidates for early mitral surgery, there is no evidence that operating earlier achieves a clinical benefit. This would require a clinical trial, which we strongly encourage. In addition, our thresholds for separating groups were derived from a single cohort without a separate validation cohort to confirm the cut points or the degree of separation. Therefore, it is likely that the degree of separation between subgroups may be lower than in this study or the thresholds for separating groups may vary. A validation cohort is required to confirm these thresholds. In addition, the use of single cut points to separate groups may underestimate the degree to which there is an incremental risk with increasing values of the parameters. Although we identified further separation with multiple thresholds for only mitral regurgitant fraction, larger sample sizes and different cohorts may reveal an incremental risk for other parameters.

The lack of blinding to the CMR data in 3 of the investigating centers may also have biased outcome. However, there are no current CMR criteria/thresholds for recommending surgery, and we attempted to minimize bias when possible and confirmed that there were no significant differences in the association with the progression to surgery between centers. Nevertheless, remaining bias is possible, particularly given the subjective nature of symptom assessment.

The echocardiographic studies were acquired for clinical purposes, and it is possible that they were not as comprehensive as those performed specifically for a research study might be. Every effort was made, however, to ensure the best-quality assessment, including blinded reanalysis by the researchers.

This study relies on events over time, and it is possible that some subjects assigned to the conservative group were censored before they had developed symptoms. However, these subjects would be likely to have higher degrees of MR, which would have likely resulted in a greater separation between groups if more time had occurred rather than a reduction in the discriminatory ability observed in the study.

We did not include data on subjects' medication, and it is possible that outcome may have been influenced by this. However, no previous studies have shown a significant effect of any drug on outcome in MR.

Conclusions

Quantification of MR with CMR showed a significant association with the future need for mitral valve surgery and was

superior to CMR-derived LV volume and echocardiographic grading of regurgitation. These CMR parameters might prove useful for identifying suitable patients for early mitral valve repair/replacement, and a randomized, controlled trial is recommended to confirm these findings and to determine clinical benefit. The same parameters may also be used to identify patients at low risk of future events, potentially facilitating reduced frequency of follow-up and efficient use of healthcare resources.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Early surgery has been advocated for asymptomatic patients with severe mitral regurgitation if valve repair is likely, but identifying suitable patients is difficult because many would remain asymptomatic for years without surgery. A greater ability to identify those who might benefit from early surgery would be highly advantageous, so we assessed the ability of cardiovascular magnetic resonance (CMR) quantification of mitral regurgitation to predict the development of symptoms or other conventional indications for surgery in the near future. One hundred nine asymptomatic patients with echocardiographic moderate or severe mitral regurgitation had baseline CMR scans and were followed up for up to 8 years. CMR quantification showed a strong ability to predict patients who progressed to require surgery: 91% of subjects with regurgitant volume ≤55 mL survived to 5 years without surgery compared with only 21% with regurgitant volume >55 mL (P<0.0001). A similar separation was observed for regurgitant fraction ≤40% and >40%. CMR-derived end-diastolic volumes and function did not add to the discriminatory power of regurgitant fraction/volume alone but are important for overall patient assessment. CMR may thus be able to identify patients likely to develop symptoms or other conventional indications for surgery in the near future, who would be an appropriate target group for early surgery, to avoid the potential reduced prognosis by the time symptoms occur. The clinical benefits of early surgery require confirmation in a clinical trial, however.

List of Figures and Tables